Ph.D. Doctoral Dissertation

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The efficacy of cold facial immersion and the diving response in treating panic disorder

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Abstract

The presence of respiratory abnormalities is quite common in panic disorder (PD) patients. A common respiratory abnormality that has been detected amongst PD patients is increased CO₂ sensitivity. Klein (1993) postulated the existence of a false suffocation alarm monitor, which is sensitive to detecting CO₂ changes, such as those that occur with panic attacks. Klein speculated that PD patients have enhanced CO₂ sensitivity of their chemical chemoreceptors, which prompts the brain’s suffocation monitor to erroneously signal a lack of oxygen and trigger a false suffocation alarm. The diving response (DR) is an oxygen conserving adaptation that is activated by apnea (breath-holding) and cold facial immersion (CFI). During the DR, individuals experience a number of physiological changes including a significant decrease in heart rate and redistribution of blood to vital organs. In many ways, the physiological changes that are experienced during the DR, a feeling of calmness and relaxation are the opposite of those experienced during a panic attack. Breath-hold divers have notably lowered CO₂ sensitivity and a more pronounced DR as a result of trained effects. Three studies were conducted examining the application of CFI and the DR in the treatment of panic disorder, and a common respiratory test used to study panic and CO₂ sensitivity, the 35% CO₂ challenge, was employed. The investigation focused on the immediate effects of breath-holding and cold facial immersion on panic symptoms and its implications in changing CO₂ sensitivity, in response to the CO₂ challenge. Significant reductions in both physiological and cognitive symptoms of panic were noted in the clinical group following the CFI task, which demonstrates promise in the utility of the CFI task. Qualitative research undertaken on the activation of the DR yielded promising results in reducing panic symptoms and eliciting calming and relaxing effects in participants. Hence, further investigation to determine the
implications of the DR in treating PD is warranted, and more specifically how CFI and alternative forms of activating the DR can be used as a potential intervention.
In accordance with Swinburne University’s Higher Degree Research Training Statement of Practice (version 5.0), I hereby declare that this thesis:

- contains no material which has been accepted for the award of any other degree or diploma, except where due reference is made in the text of the examinable outcome;
- to the best of my knowledge, contains no material previously published or written by another person except where due reference has been made in the text of the examinable outcome, and
- where the work is based on joint research or publications, full disclosure of the relative contributions of the respective workers or authors has been made.

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__________________________
Peter Kyriakoulis
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<td>ACT</td>
<td>Acceptance and Commitment Therapy</td>
</tr>
<tr>
<td>ANS</td>
<td>Autonomic Nervous System</td>
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<tr>
<td>AS</td>
<td>Anxiety Sensitivity</td>
</tr>
<tr>
<td>BNST</td>
<td>Bed nucleus of the stria terminalis</td>
</tr>
<tr>
<td>BH</td>
<td>Breath-hold</td>
</tr>
<tr>
<td>BHT</td>
<td>Breath-hold training</td>
</tr>
<tr>
<td>BT</td>
<td>Breathing training</td>
</tr>
<tr>
<td>CO₂</td>
<td>Carbon Dioxide</td>
</tr>
<tr>
<td>CeA</td>
<td>Central Nucleus of Amygdala</td>
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<td>CNS</td>
<td>Central Nervous System</td>
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<td>CBT</td>
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<td>CFI</td>
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<td>DR</td>
<td>Diving Response</td>
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<td>DPAG</td>
<td>Dorsal Periaqueductal Gray</td>
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<td>DMH/PeF-</td>
<td>Dorsomedial perifornical hypothalamic</td>
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<td>PFC</td>
<td>Pre-frontal Cortex</td>
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<tr>
<td>PNS</td>
<td>Parasympathetic Nervous System</td>
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<td>Partial pressure of oxygen</td>
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<td>PAG</td>
<td>Periaqueductal Grey</td>
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<td>SNS</td>
<td>Sympathetic Nervous System</td>
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<td>VLPAG</td>
<td>Ventro lateral periaqueductal gray</td>
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Overview of Thesis

Panic disorder (PD) is one of the most common anxiety disorders. It is characterised by recurrent panic attacks, is often disabling, and usually follows a chronic course if left untreated (Kessler et al., 2014). Frequently treatments are ineffective and costly, hence greater knowledge of the underlying pathophysiology of PD is required to assist with the development of effective treatments (Wemmie, 2011). Panic attacks (PAs) are experienced as highly distressing and are often accompanied by a fear of impending doom, and a myriad of emotional, physiological, behavioural, and cognitive symptoms. The pronounced bodily symptoms are often misinterpreted as indications of somatic or mental illness, such as having a heart attack or going crazy. Among the scariest of symptoms are the elevated heart rate and the dysregulation of the autonomic nervous system.

Free diving is the sport of diving underwater on one single breath. It has been characterised as calming and relaxing, inducing physiological effects that are opposite to those experienced when having a panic attack. The key factors common to both free diving and PAs are mental control and breathing control. Hence, it is plausible that there is something to be learnt from the physiological adaptions and techniques used in the sport of free diving, to assist individuals in better managing PAs. The diving response (DR) is an innate human physiological adaptation that helps conserve oxygen and increase breath-hold time under water. Free divers are known to be a unique group of individuals as they do not only have exceptional breathing control but also a pronounced DR as a result of trained effects (Schagatay, 2002).
Chapter 1 provides a comprehensive overview of PD. The primary focus of Chapter 1 is on the clinical phenomenology of PD, including current theoretical understanding of the aetiology of PD. This chapter includes discussions of the disorder’s diagnostic criteria, pathophysiology and the various theories that explain the aetiology of PD, with a particular focus on the neuroanatomical theory of PD. Various treatments of PD are also discussed including psychological and physiological interventions.

Chapter 2 introduces the notion of apnea, cold facial immersion (CFI) and the human adaptation known as the diving response (DR). The cardiorespiratory mechanisms and physiological responses of the DR are discussed. This chapter also focuses on discussing breath-holding and cold facial immersion as a way of eliciting the DR. The sport of free diving is also introduced, with a particular focus on the research regarding the physiological responses observed in free divers who are trained in breath-hold diving, and whom demonstrate extraordinary trained effects with regard to the DR. This research is used to explore the clinical implications of the DR as valuable in the treatment of PD.

Chapter 3 discusses the relationship between respiration, anxiety, and PD. This chapter provides an overview of the physiology, the mechanics of breathing and discusses breathing and chemosensitivity in relation to PD. Cardiorespiratory abnormalities and homeostatic disturbances and their link to PD are also explored. Furthermore, respiratory provocation tests are discussed in terms of how they complement the pathophysiology of PD.
Chapter 4 presents the preliminary study, Respiratory Challenges, and Cold Facial Immersion. The chapter provides a summary of the study aims, hypotheses, the planned research design, outlining participant details, and research procedures. A number of research questions arise from the literature review, including how individuals that suffer from PD differ in their cardiorespiratory response to normal individuals on a number of respiratory challenges such as breath-holding, the 35% CO₂ challenge, cold facial immersion (CFI) and the CO₂ plus CFI task. Another research question that the preliminary study sets out to investigate is whether the DR, when activated via CFI, can reduce panic symptoms and cognitions. This chapter also presents the results and discussion of this preliminary study. CFI is demonstrated to have a powerful response in reducing panic symptoms, hence the research set out to investigate whether CFI may be able to change CO₂ sensitivity in response to the CO₂ challenge. This chapter also discusses methodological considerations and improvements for the subsequent study.

Chapter 6 provides an overview of study aims, hypotheses, the planned research design, outlining participant details, and research procedures of the second research study examining the effects of cold facial immersion on CO₂ sensitivity. This study explores the CO₂ sensitivity in clinical and control participants and the reduction of panic and anxiety symptoms following CFI and the activation of the DR. This chapter also presents results and discussion of this study. The findings do not support the short-term application of CFI (one single exposure). However, the findings indicate decreased physiological and psychological symptoms anxiety/panic and warrants further investigation of its applications.
Chapter 7 presents a qualitative exploration of panic and cold facial immersion (CFI). The chapter presents a thematic analysis of the common symptoms of panic for the clinical participants and ways that they currently try to manage their symptoms. Thematic analyses of all participants experience of cold facial immersion are also presented, along with key challenges identified with its use as an intervention and its utility from the perspective of their experience of the task. Given that CFI may not always be easy nor practical to use, the key challenges, benefits and alternative applications of how CFI can be used as an intervention are discussed including alternative methods for activating the DR.

Finally, Chapter 8 presents the overall thesis conclusions including a discussion and implications of all studies of the research and future directions.
Chapter 1

PANIC DISORDER

Panic disorder (PD) is a severe and highly distressing prevalent anxiety disorder characterised by spontaneous and recurrent panic attacks (PAs) (5th ed.; DSM-5; American Psychiatric Association, 2013). It is characterised by a high degree of subjective distress and is commonly occupationally and socially disabling (Goodwin et al., 2005; Klerman et al., 1991; Wittchen, 1998). In terms of years of life lived with disability rates, anxiety disorders ranked as the sixth leading cause of all disability, with panic disorder (PD) being amongst the highest of the anxiety disorders, accounting for more disability than severe mental disorders such as major depressive disorder and schizophrenia (Baxter, Vos, Scott, Ferrai & Whiteford, 2010).

PD is among the anxiety disorders that can have a significant impact and debilitating effect on peoples’ lives and has resulted in elevated levels of social, marital, occupational and physical disability (Klerman, Weissman, Oulette, Johnson & Greenwald, 1991). In both the primary health-care and community settings it is regarded as one of the most costly mental health conditions (Kessler et al., 2005; Meuret et al., 2017), carrying significant economic costs (Roehrig, 2016). While the lifetime prevalence of PD (4.7%) (Meuret, Kroll & Ritz, 2017) is lower than that of other anxiety disorders, it is still high. In particular, the prevalence of subthreshold PD and PAs (22.7% lifetime) are very high (Roy-Byrne et al., 1999) and associated with high individual and social costs (Batelaan et al., 2007; Kessler et al., 2006).
1.1 PANIC DISORDER AND PANIC ATTACKS

Panic disorder was initially classified as a distinct nosological entity in the third edition of the DSM (APA, 1980). The core syndrome and defining feature of PD is a panic attack and in particular spontaneous panic. Spontaneous panic is unexpected, as distinct from cued (expected) panic, and can occur at any time (Schmidt, Lerew, & Jackson, 1997). PAs are characterised as intense and unexpected fear responses to perceived threat that may include external stimuli (e.g., predators), or internal stimuli arising in the body, also known as interoceptive signals (e.g., racing heart), nociceptive triggers (e.g., painful stimuli), or threatening conspecifics (e.g., rivals) (Hamm et al., 2016). A panic attack has been defined as a discrete period of intense dread or fear, accompanied by a number of physical and cognitive symptoms (American Psychiatric Association, 2013), which are depicted in Figure 1.

PAs are a strong predictor in the subsequent development of a range of psychological disorders such as mood disorders and anxiety disorders including but not limited to PD (Baillie & Rapee, 2005; Barlow 2002; Goodwin et al., 2005, Kinley et al., 2011). As a result of its sudden or unexpected onset and brief length, it is discrete as distinct from progressively building anxious arousal (Craske & Barlow, 2001). Sufferers of PD experience sudden and repeated PAs which are marked by a fear of imminent danger or impending doom and an urge to flee, even in non-dangerous situations. Like all basic emotions, strong action tendencies are associated with PAs, including urges to escape, and to a lesser extent urge to fight. Hence, PAs are believed to activate the fight or flight response, an autonomic reaction that is activated in response to a perceived threat, or danger (Craske & Barlow, 2001).
Figure 1. Physical and cognitive symptoms of panic disorder.
Typically, intense fear experienced during PAs peaks in less than 10 minutes and subsides in 30 minutes (American Psychiatric Association, 2013; Graeff, 2016). PAs are characterised by acute physical symptoms which can include respiratory, cardiovascular, vestibular and gastrointestinal symptoms (i.e., dyspnea, pounding or racing heart, sweating, dizziness, chills, tingly or numb hands, chest/stomach pain, abdominal discomfort) and psychological symptoms (i.e., fear of losing control, fear of dying and fear of going crazy) (American Psychology Association, 2013; Goodwin et al., 2005; Graeff, 2016).

In PD, panic attacks often have an unexpected quality, as they commonly occur without an obvious trigger and resulting in individuals worrying and dreading the possibility of having another attack (Craske & Barlow, 2001; Kircanski, Phil, Craske, Epstein, & Wittchen, 2009). One such example is nocturnal panic, which refers to waking abruptly from sleep in a state of panic, with no obvious trigger. Nocturnal PAs are frequently experienced by individuals with PD (Craske & Tsao, 2005). More often, nocturnal PAs emerge from non-rapid eye movement (NREM) sleep and thus are not commonly preceded by dreams (Barlow, 2014; Craske & Barlow, 2007; Craske & Tsao, 2005). They are usually characterised by sudden awakening, terror and intense physiological arousal. Most PD sufferers describe the nocturnal attacks as less intense, with fewer symptoms, and less severe than the diurnal PAs (Craske & Barlow, 1990). Panic attacks may even occur during states of relaxation (Adler et al., 1987; Cohen et al., 1985).
1.2 THE AETIOLOGY OF PANIC DISORDER

There are a range of theories which have sought to explain the development of PAs and PD. Currently, there are five prominent theories that have been applied to understanding the origins of PD. Broadly speaking theories of PD tend to fall into two categories: psychological and biological theories and include conditioning (Goldstein & Chambless, 1978) and related theories; cognitive theories (Beck & Emery, 1985; Clark, 1986, 1988; Clark, 1996), anxiety sensitivity theory (McNally, 1994; Reiss, 1991), psychodynamic theories and biological theories, which encompass neurobiological and neurochemical factors, metabolic and genetic theories, respiratory and hyperventilation theories (Nardi & Freire, 2016).

1.2.1 Psychological Theories of PD Aetiology

1.2.1.1 Conditioning Theories

Conditioning theories have a long history in assisting the understanding of anxiety disorders (Eysenck, 1979; Marks, 1969; Wolpe & Rowan, 1988) and were among the first type of theories applied to examine the aetiology of PD (Eysenck, 1960; Eysenck & Rachman, 1965). According to conditioning theories, when stimuli, events or situations, known as conditioned stimuli (CS), are paired with a panic attack (PA) (including its somatic symptoms), learning may occur that results in the CS triggering panic and anxiety when they are encountered again. During a PA, stimuli from both the internal and external environments can become associated with panic via the process of classical conditioning (Barlow, 2000; Battaglia and Ligari, 2005; Bouton, Mineka and Barlow 2001; Goldstein & Chambless, 1978) and may subsequently elicit a conditioned response (CR) of either anticipatory anxiety or preceding panic (Bouton et al., 2011). This general theory has been applied to PD in
various ways with the most noted work being that of Goldstein and Chambless (1978) who coined the term “fear of fear”. Goldstein and Chambless (1978) posited that PD patients learn to fear symptoms of anxiety through interoceptive classical conditioning of internal physical sensations. Hence, fear of fear develops as a result of having PAs. Following Goldstein and Chambless’ (1978) theory, the focus for conditioning theory changed from exteroceptive conditioning (i.e., external triggers) used to understand agoraphobia and situational panic to interoceptive conditioning (i.e., internal bodily triggers) that more effectively assisted in understanding the cause of “spontaneous” PAs or those that occur in the absence of an obvious trigger.

Various criticisms of early conditioning theories have been noted in the literature. Interoceptive conditioning has been criticised as being conceptually confusing due to panic and anxiety appearing to serve as CS, unconditioned stimuli (US), conditioned response (CR) and unconditioned response (UR) indiscriminantly (McNally, 1990, 1994; Reiss, 1987). Conditioning theory has also been criticised for overpredicting panic; in theory, a fear or panic response should happen every time the CS is encountered (e.g., a somatic symptom, such as sweating) (Clark, 1988).

Another criticism points to the observation that the fear or panic response does not seem subject to extinction in trials that demonstrate that arousal and the somatic sensations it generates are not followed by panic (Rachman, 1991; Seligman, 1988; Van den Hout, 1998).
1.2.1.2 Modern Learning Theory

A more modern perspective on classical conditioning and its many effects on emotion and behaviour was proposed by Bouton et al. (2001), whose perspective builds on growing evidence that anxiety and panic are at least partially unique experiences. Research examining anxiety and panic related symptoms reveal these two constructs are separate aspects of PD. That is, panic is accompanied by strong autonomic arousal, extreme fear, and fight or flight response tendencies, whereas anxiety is accompanied by apprehension, worry and tension (Barlow, 1988; Craske, 1999). Anxiety is seen as preparing the system for an anticipated trauma, whereas panic deals with the one that is already in progress (Bouton et al., 2001). Panic and anxiety are therefore different and this perspective is also consistent with neurobiological research that supports the partially distinct emotional states of anxiety and panic (e.g., Fanselow, 1994; Tovote, Fadok & Luthi, 2015). Hence panic or fear allows the individual to combat or avoid/escape immediate threats or danger, whereas anxiety increases vigilance and improves one’s ability to identify potential threats, both serving important evolutionary functions in line with keeping the individual safe (Duval, Javanbakht & Liberzon, 2015).

According to this perspective, a central factor in the development of PD is the interaction of anxiety and panic. Anxiety may manifest as anticipatory anxiety and thus contributes to PD maintenance via a positive feedback loop of anxiety and panic (Barlow, 2000; Öhman et al., 2001). Bouton et al. (2001) propose that anxiety potentiates panic, and the development and presence of conditioned anxiety, which in turn exacerbates subsequent PAs. In keeping with earlier approaches to PD, Bouton et al.’s. (2001) perspective also highlights the fundamental role of early conditioning.
They maintain that the conditioning that may occur during initial PAs in vulnerable individuals sets the scene for the development of PD. Thus, these PAs become associated with initially neutral interoceptive conditioned stimuli (CS) (i.e., heart palpitations, dizziness) and exteroceptive CS (i.e., escalators and supermarkets) through the associated learning process known as classical conditioning. For instance, an individual who is sensitive to the sensation of their rapidly beating heart may experience a panic attack at a time when they are happy and experiencing excitement, as this is also a time when heart racing can occur and, hence in this instance, it may serve as an interoceptive CS (Mineka & Zinbarg, 2006). Furthermore, via the process of stimulus generalisation, autonomic constituents of panic (e.g., irregular heart rate or the feeling of shortness of breath) may generalise to similar non–arousal sensations (e.g., exercise–induced sensations) (Lissek et al., 2010; White et al., 2006). Thus, through the proliferation of cues that trigger anticipatory anxiety and panic, the initial spontaneous PAs may evolve into PD (Barlow, 2000; Bouton et al., 2001; Lissek et al., 2010). The crucial feature here is the idea that the conditioned anxiety that comes to be elicited by interoceptive and exteroceptive cues associated with panic serves to amplify future panic reactions. Hence, anxiety becomes an antecedent of panic (Bouton et al., 2001).

Some limitations have been noted with the learning theory of PD. Firstly the onset symptoms in PD tend to develop usually at the same time, rather than one by one, like in a vicious cycle pattern. This may explain why PAs do not always occur following dangerous situations e.g., after a near miss car accident. Furthermore, despite experiencing countless PAs which demonstrate that symptoms do not result in dangerous outcomes, PD sufferers fail to learn and continue to fear their symptoms as
being unsafe. This evidence lends further support to the argument that PAs are merely due to false learning processes (Bandelow, Domschke & Baldwin, 2014). Associative learning deficits in the learning of panic-cue relationships may render PAs unsignalled and unpredictable in PD (Grillon, et al., 2007). Moreover, PAs usually occur during a state of very low activity characterised by NREM sleep, where cognitive processes are likely to be limited (McNally, 1994). Interoceptive conditional responses are an example of this as they are not always dependent on conscious awareness of triggering cues, but rather once acquired, these responses can be elicited under sleep or anaesthesia (Craske & Barlow, 2007).

1.2.1.3 Cognitive Theories

Cognitive theories identify the “catastrophic misinterpretations” of an individual’s own bodily symptoms and sensations as being pivotal to both the development and maintenance of PD (Beck & Emery, 1985; Clark, 1986, 1988; Clark, 1996; Otto & Pollack, 2009; Salkovskis, 1988). According to this perspective, panic develops when an individual focuses on his or her internal physical sensations irrespective of whether they are produced by anxiety, which in turn leads to catastrophic thoughts about their impending meaning, such as “I am having a heart attack” or “I am dying”. The catastrophic thoughts, which in themselves are anxiety provoking produce further somatic symptoms. This leads to more catastrophic thinking, thus fuelling a vicious cycle that inevitably ends in a panic attack. According to cognitive theories, it is the individual’s focus on internal bodily symptoms and sensations that lead to persistent vigilance and hypersensitivity to normal and common physical sensations (Bouton et al., 2001). Further support for the cognitive theory is provided by a causal link between physiological sensations and
fearful thoughts (Rachmann, Levitt & Lopatka, 1987). For instance, reading paired word combinations related to somatic sensations and catastrophes (e.g., “palpitations – die” and “breathless – suffocate”) has been found to increase the likelihood of PAs (Clark, 1988). On the other hand, when catastrophic misinterpretations are reduced, the likelihood of panic in response to panic provocation agents also decreases (Clark, 1996). Cognitive behavioural therapy has demonstrated efficacy in managing PD and given it is proposed to target maladaptive cognitive processes this lends support for the cognitive theory in the aetiology of PD (eg., Allen and Choate 2016; Clark et al., 1994; Chen & Tsai, 2016; Barlow, 2000).

Whilst support has been found for cognitive explanations of PD, Bouton et al. (2001) have highlighted limitations. Catastrophic cognitions are often found to occur in patients suffering from PD. Although their causal role in creating PAs is ambiguous, the persistence of such catastrophic cognitions facilitates the maintenance of PD as sufferers engage in safety seeking behaviour and escape and/or avoid situations where panic occurs (Salkovskis, Clark & Gelder, 1996). According to Bouton et al. (2001), key concepts such as “catastrophic misinterpretations” are considered vague as it is difficult to determine how they are acquired and measured and who is likely to acquire these. Cognitive theories do not account for the distinction between the emotional states of anxiety and panic, despite there being emerging evidence to the contrary, (i.e., as supported by anxiety sensitivity theory).

A large body of research has demonstrated a relationship between anxiety sensitivity and panic–related psychopathology (Bouton et al., 2001; Dixon, Sy, Kemp & Deacon, 2013; McNally, 1994, 2000; Reiss, 1991; Poletti et al., 2015; Reiss &
findings from various sources including correlational studies, provocation tests, intervention research, and prospective studies are suggestive that the fear of anxiety–related somatic sensations play a crucial role in panic psychopathology (Dixon et al., 2013). Nelson, Hodges, Hajcak, and Shankman (2015) reported in their study that the different anxiety sensitivity dimensions have distinct relationships with the “acute” and “potential” threat (i.e., fear and anxiety respectively). Various researchers have indicated cognitive and personality factors (Craske & Waters, 2005; Mathews & MacLeod, 2005; Watson & Clark, 1984) that may place individuals at risk for the vigilance and misappraisals. In particular, “anxiety sensitivity” has been touted as one such vulnerability factor (Olatunji & Wolitzky-Taylor, 2009).

1.2.1.4 Anxiety Sensitivity Theory

Anxiety sensitivity (AS) refers to the extent to which an individual believes that their own bodily sensations and symptoms can have harmful consequences and, as a construct, it is closely linked with fear of fear (Reiss & McNally, 1985). Individuals with high AS may attribute shortness of breath to suffocation, or heart palpitations to heart attack, as compared to individuals with low AS who may experience discomfort but do not perceive sensations as threatening. Similarly to cognitive theories of panic, AS posits that cognitive misappraisal is key to the provocation of anxiety. Conversely, AS theory is distinguished from other perspectives by virtue of its belief that AS is an enduring trait-like characteristic that may precede the development of PAs. Furthermore theorists of AS (McNally, 1994; Reiss, 1991) contend that individuals suffering PD often do not misinterpret the causes of their sensations and are fully aware of them, but maintain their fear as a
result of intrinsic beliefs about the possible harm of sensations to their body or mental health (Bouton et al., 2001).

Whilst research has demonstrated support for the AS theory (Hayward, Killen, Kraemer, & Taylor, 2000; Schmidt et al., 1997; Schmidt, Lerew, & Jackson, 1999), what AS specifically predicts is questionable. Bouton et al. (2001) have indicated that an empirically identified relationship between AS and PAs is small in many studies (see also Schmidt et al., 1997, 1999; Weems, Hayward, Killen & Taylor, 2002). Another point of criticism is that these studies have evaluated how AS may predict PAs and worry about panic, rather than diagnosed PD. Furthermore, the work of Hayward et al. (2000) challenges the notion of whether AS is the best predictor of unexpected panic in comparison to negative affectivity. Hence, the causal significance of AS of PD is not clearly defined in the literature. Although Dixon, et al. (2013) in their study provided support that AS induced experimentally causes the subsequent development of anxiety and panic. Panic sufferers are known to overreact to bodily signs (Clark et al., 1997), which may be due to an anomaly in brain structures such as the insula and the anterior cingulate gyrus which are responsible for interoceptive integration (Uchida et al., 2008). In terms of anxiety sensitivity, the sensation of suffocation is amongst the internal stimuli that seem to be related and particularly important for panic patients (Klein, 1993).
1.2.2 Biological Theories of PD Aetiology

1.2.2.1 Genetic Theories

Genetic and family studies are amongst the most prominent biological theories suggesting that PD appears to run in families and that individuals who suffer from PD may have an inherited genetic predisposition. Crowe, Noyes, Pauls and Slymen (1983) studied the prevalence of PD among families of PD patients and found that approximately 25% of patients with a diagnosis of PD had first degree relatives with PD. Further evidence suggests that amongst first degree relatives of PD patients, up to threefold increases in prevalence have been observed (Maier et al., 1993; Nocon et al., 2008). Family and family history studies undertaken cross-culturally point to a strong genetic influence being noted between first degrees relatives that have PD and agoraphobia (Batagglia & Ogliari, 2005; Crowe et al., 1983).

Twin studies have also provided us with valuable information. Torgersen (1983) examined concordance rates of anxiety disorders with PAs and reported in his findings that 31% of the monozygotic twins had a similar diagnosis to each other compared to 0% of the dizygotic (DZ) twins. One twin study that compared CO₂ responsiveness among monozygotic and dizygotic twins found greater concordance rates for monozygotic twins for panic induced by CO₂ challenge (Bellodi et al., 1998). Overall studies demonstrate 2-3 times higher concordance rates among dizygotic than among monozygotic twins, lending support for there being a genetic contribution to the development of PD (Shih et al., 2004). Other twin studies have proposed a link between genetic factors and the pathogenesis of PD with heritability contributions, ranging from 30-48% for PD and over 50% for agoraphobia (Hettema et al., 2001; Kessler et al., 2005).
A meta-analysis of three twin studies reported a genetic contribution to the presence of PD of 43% (Hettema et al., 2001). Battaglia and Ogliari (2005), in reviewing the literature confirmed that the moderate to high heritability estimates are largely due to genetic influences, rather than environmentally shared influences. Panic attacks were more than five times more frequent in monozygotic twins than in dizygotic twins of patients with PD. However, the findings of this particular review may not be conclusive as they only used a small number of twins and the results may be explained by the fact that monozygotic twins share more similar environmental experiences and are commonly treated more similarly than dizygotic twins (Maier, Lichtermann, Minges, Oehrlein, & Franke, 1993).

Childhood separation anxiety disorder has also been known to correlate with the increased early onset of PD and increased family loading (Battaglia et al., 1995; Lipsitz et al., 1994). Robertson-Nay et al. (2012) in their twin studies demonstrated a shared common genetic diathesis between adult onset PAs and childhood separation anxiety disorder, suggesting a genetic etiologic link between the two phenotypes. Criticisms of genetic theories have included failure to yet identify a mode of inheritance in line with Mendelian patterns, thus pointing to an intricate genetic inheritance model with interactions of multiple vulnerabilities and genes (Bandelow et al., 2013). To date, only a very small number of risk genes have been identified with not much known about gene-environment interactions specific to PD.

1.2.2.2 Hormone Theory

It has been well documented that hormones, particularly gonadal hormones, play a significant role in influencing the frequency and intensity of PAs. Spontaneous
PAs affect more women than men, and it is thought that in women the occurrence of PAs may be linked to the production of reproductive hormones as they rarely start before puberty or after menopause (Klein, Mannuzza, Chapman & Fyer, 1992). Interestingly, a marked decrease of panic has been observed in PD patients during pregnancy, delivery, and lactation, followed by post lactational exacerbation of panic symptoms (Bandelow et al., 2006). These changes are related to increased levels of estrogen, progesterone, and oxytocin during pregnancy and breastfeeding (Klein, 1993). Despite the pregnancy and childbirth period being thought of as one with marked and heightened anxiety and common catastrophic interpretation of physiological changes, PAs are less frequent and intense during this period, suggesting that possibly some of the pregnancy hormones may serve to be protective of PAs (Bandelow et al., 2006; Klein, 1993).

1.2.2.3 Metabolic Theories

Metabolic theories have also been popular with people who have a diagnosis of PD being more sensitive to certain substances including injections of lactic acid, elevated CO₂ levels, caffeine, yohimbine, m-cholorophenylpiperazine, cholecystokinin, nicotine, and alcohol than are their non–panic counterparts (Bourin et al., 1997). Researchers have used various procedures in an attempt to reproduce panic like symptoms in order to understand the aetiology of PD, including both biological and cognitive models of panic. Cognitive factors such as sense of control (Sanderson, Rapee & Barlow, 1989), persistence of catastrophic thinking (Clark, 1986) and anxiety sensitivity (McNally, 1989) are amongst some of the psychological factors that are known to influence one’s response to the CO₂ challenge (Carter, Hollon, Carson & Shelton, 1995).
Some of the earlier chemicals to trigger panic-like symptoms in experimental settings with humans included epinephrine and norepinephrine (Lindemann, 1935; Lindemann & Finesinger, 1938; Wearn & Sturgis, 1919). Cholinergic agents have also been used including parasympathomimetic methacholine and cholinesterase inhibitor physostigmine in some studies (Lindemann & Finesinger, 1938; Paul & Scolnick, 1981; Risch et al., 1981). Among the most common procedures used include the pharmacological agent sodium lactate (Appleby et al., 1981; Haslam, 1974; Liebowitz, Gorman, Fyer, Dillon, & Klein, 1984; Pitts & McClure, 1967) and hyperventilation and CO₂ challenges (Gorman et al., 1984; Papp et al., 1989; van de Hout & Griez 1974). Charney et al. (1984a) and Uhde (1990) were able to demonstrate that caffeine challenge tests induce panic-like symptoms suggesting a potential implication of the adenosine system in explaining panic and anxiety. Adenosine receptors are located and dispersed in all brain areas and regulate the release of neurotransmitters and the action of neuromodulators (inhibitory and excitatory functions) (Sebastiao & Ribeiro, 2009). Alternative procedures used have included the administration of cholecystokinin tetrapeptide (CCK4) (Bradwejn et al., 1991, 1992; Bradwejn & Kozycki 1994a; Bradwejn & Koszycki, 1994b), yohimbine, flumazenil, β-carboline, isoproterenol, piperoxan which act on the noradrenergic or adrenergic systems (Charney, Woods, Goodman & Heninger, 1987; Charney et al., 1990; Graeff, Garcia-Leal, Del-Ben & Guimaraes, 2005; Olpe et al., 1983; Pohl et al., 1990).

Animal studies and brain imaging techniques such as fMRI (functional magnetic resonance imaging), MRI, PET (positron emission tomography), SPECT (near infrared spectroscopy) and electrical and chemical stimulation, as well as
electrical recording, have also been used extensively in recent years to identify specific brain regions which are implicated in the regulation of panic and anxiety (Dresler et al., 2013; Duval, Javanbakht & Liberzon, 2015). Lueken et al. (2014), in their study, found that the amygdala, hippocampus, and midbrain were amongst the brain structures that were activated in specific phobia. A breakthrough in furthering our understanding of panic occurred in the 1980s when it was observed that clinical panic, as well as panic induced in the laboratory by lactate injections, did not activate the hypothalamus-pituitary-adrenal (HPA) axis (Levin et al., 1987). Hence this discovery differentiated stress like reactions and common fear from clinical panic.

For decades, the HPA axis (neuroendocrine stress system) activity has been extensively investigated in patients with psychiatric illnesses, namely depression and anxiety disorders (Abelson et al., 2007). More recently studies addressing the HPA-system’s functioning in anxiety disorders have yielded mixed results (Bosch et al., 2012; Plag et al., 2013), however it reported a general finding of increased basal levels of cortisol in patients suffering from PD and HPA axis activation at both the pituitary and the adrenal level (Van Duinen, et al, 2007).

Cognitive behavioural therapy and physical exercise have been shown to alter the activity in the HPA system, specifically decreasing corticotrophin (ACTH) and cortisol plasma-levels in response to a pharmacological panicogenic challenge (Abelson et al., 2005). Several studies reported similar findings investigating the short-term beneficial effects of physical exercise on the stress response (Deuster et al., 1989; Lucia et al., 2001; Luger et al., 1987; Uusitalo et al., 1998). Plag et al. (2014) provided evidence for a deferred and differential effect of endurance training on the HPA stress response in both PD with and without agoraphobia. While results have
been inconsistent, these studies have nevertheless revealed that patients with PD suffer from HPA axis dysregulation (Abelson et al., 2007).

Despite inconclusive evidence whether the HPA axis is implicated in PD or not, there is an emerging consensus that there are some key areas in the brain involved in PD. Amongst the regions of the brain that are commonly identified to play a crucial role in PD include the limbic area, particularly the amygdala, which is directly associated with the fight or flight response (Schenberg, 2010), and the locus coeruleus (LC), which appears to be involved in the sleep-wake cycle, arousal, anxiety and fear (Redmond et al., 1976; Redmond & Huang, 1979). Other important areas that appear to be implicated in the modulation of anxiety include the hypothalamus, pituitary gland, especially anterior pituitary gland. These regions are responsible for both the synthesis and release of stress related hormones (Tsigosa & Chrousos, 2002).

The observation that stress hormones including corticotrophin, cortisol and glucocorticoids and prolactin remain unaltered during PAs provide us with a vital clue in understanding the neurobiology of PD (Schenberg, 2010). Goosens et al. (2014), investigated differences in three groups with descending sensitivity to CO₂; panic patients, healthy individuals, and experienced divers. They concluded that the behavioural response that characterises PD patients is predominantly due to the neural sensitivity to CO₂ located in the brainstem area. To date, three brainstem areas involved in both panic and chemosensitivity have been identified, these include the periaqueductal gray (PAG), the raphe nuclei (RN), and the locus coeruleus (LC) (Goosens et al., 2014). The LC which is located in the brain stem is a tiny nucleus which contains 70% of all noradrenergic neurons in the brain. When stress activates
the LC it results in increased noradrenaline release in LC projection sites including the amygdala, pre-frontal cortex, and hippocampus (Charney, 2004). In animal studies and in vitro studies, where molecules or cells may be studied outside their natural environment, CO₂ may directly activate neurons in the LC. Although direct in vivo evidence in humans presently does not exist, Bailey et al. (2003) speculate that CO₂ effects may be mediated via the noradrenergic network. The noradrenergic theory of PD which suggests an abnormal central noradrenergic function in PD patients has been criticised by researchers, contending that the LC mediates arousal rather than panic and sympathetic nervous system arousal (Samuels & Szabadi, 2008).

The PAG has also been implicated in the pathogenesis of panic, given that patients that were awake whilst undergoing neurosurgery involving electrical stimulation of the PAG, elicited symptoms remarkably similar to those reported by PD patients when enduring a panic attack (Del-Ben & Graeff, 2009). These findings support the notion of a continuous trait, based on one’s individual sensitivity response to increasing concentrations detected of CO₂ (Pine et al., 2000).

1.2.2.4 Neurochemical Theory

One prominent biological theory proposes that symptoms are caused by an imbalance of one or more neurochemicals including serotonin, norepinephrine, dopamine and gamma-amino butyric acid (GABA) that act as neurotransmitters in the brain (Bourin, Baker & Bradwejn, 1998). Support for this theory is evidenced by a reduction of symptoms that many patients who suffer from PD experience when taking an antidepressant or anxiolytic medication (Nutt, 2005).
In an attempt to explain the aetiology of PD, neurochemical theories propose a deficiency in the serotonergic system or excess serotonin (Graeff, 2012). Other neurochemical theories have implicated increases in the concentration of the neuropeptide Y (NPY) in anxiety circuits which has been thought to be involved in the consolidation of fear memories (Bandelow, Baldwin & Zwanzger, 2012; Bandelow et al., 2013). NPY is a 36 amino acid peptide that is strongly expressed in the cortical, limbic and hypothalamic regions of the mammalian brain (Allen, Adrian, Allen, Tatemoto, & Crow, 1983). In particular, it is considered to be the most widely expressed peptide in the brain and it can be found, in the basal ganglia, hypothalamus, hippocampus, amygdala, nucleus accumbens, cortex, periaqueductal grey and the lower brain stem (Adrian, Allen, Bloom, Ghatei & Rossor, 1983; Allen et al., 1983). Evidence suggests that NPY possesses anxiolytic properties and functionally serves the role as a protective neurochemical to facilitate stress resilience (Enman, Sabban, McGonigle & Bockstaele, 2015). In the central nervous system (CNS), NPY plays a vital role in energy homeostasis, pain, control of food intake and physiological processes related to stress/stress resilience (Enman et al., 2015). Patients with anxiety disorders have shown reduced concentrations of NPY, hence making them more sensitive to stress and fear responses (Bandelow et al., 2013).

Among some of the neurochemical theories that have been proposed to explain the aetiology of PD include a deficiency in the serotonergic system or excess serotonin (Graeff, 2012), which may convey significant vulnerability as well as adaptive factors. Johnson, Lowry, Truitt, and Shekhar (2012), attributed panic attack vulnerability to faulty serotonergic inhibition of the dorsal periaqueductal grey (DPAG) and autonomic medullary centers. Furthermore, a dysfunction in the
endogenous opioid system was proposed by Preter and Klein (2008), which decreases the threshold of the suffocation alarm. This hypothesis was supported by the findings of Preter et al. (2011) who demonstrated that lactate infusions produced symptoms that mimic those of PAs.

GABA is synthesized and released throughout the brain and is one of the major inhibitory neurotransmitters in the CNS. GABA is strongly associated with PAs and PD and it has been noted that panic patients have GABA activity deficits (Johnson, Federici & Shekhar, 2014). Research by Nikolaus et al. (2010) has demonstrated that patients with PD show reduced GABA_A receptor binding in the frontal cortex and a study by Goddard et al. (2001) discovered deficits in the central GABA concentrations in panic patients.

1.2.2.5 Respiratory and Hyperventilation Theories

Respiratory and hyperventilation theories also fall under the neurobiological theories, which attempt to explain the aetiology of panic. These theories propose that PAs may be caused by a dysfunctional respiratory system (Freire & Nardi, 2012; Gorman et al., 1984; Griez, Lousberg & Van den Hout, 1987; Woods et al., 1986). In particular, it has been proposed that hyperventilation may be causally related to PAs, given that during hyperventilation an imbalance occurs between O_2 inhaled and CO_2 exhaled, thus reducing CO_2 levels in the body (Cowley & Roy-Byrne, 1987). Individuals who hyperventilate in an attempt to compensate for the reduction in respiratory rate experience secondary symptoms, which include shortness of breath, dizziness, trembling, and palpitations (Freire & Nardi, 2012; Papp, Klein & Gorman,
It is important to note that these symptoms are also common to anxiety and PAs.

Such findings led Klein (1993) to propose that the essential disturbance in PD may be a dysfunctional suffocation monitor (a "suffocation false alarm") (SFA), in which dyspnea is the dominant symptom. High CO₂ levels usually serve as a marker that the individual is in danger of imminent suffocation since increased levels of CO₂ correspond with decreased levels of O₂. According to Klein (1993), this suffocation threshold is pathologically lowered in PD patients (i.e., SFA hypersensitive to CO₂), with increased levels of CO₂ becoming a signal for low O₂ supply. As a result, the brain's suffocation monitor incorrectly misfires and signals a lack of O₂, triggering an SFA. Klein’s hypothesis is that since PD patients believe they are suffocating, they experience shortness of breath and as a result begin hyperventilating in order to keep CO₂ levels well below the (abnormally low) suffocation threshold. Therefore, rather than causing PAs, hyperventilation is a consequence and actually a defense against the onset of panic (Klein, 1993). Breathing mechanisms are considered to be under the management of a widespread cortical and subcortical network, involving structures from the medulla, up to the hypothalamus, limbic area, and cortex.

The respiratory drive is largely controlled by the ventral respiratory nuclei (VRN) located in the medulla. The VRN control phrenic nerve activity and sense pH and CO₂ levels of cerebrospinal fluid (Loeschcke, 1982; Ter Horst & Streefland, 1994). Schenberg (2010) postulated that the SFA hypothesis deduces that the suffocation false alarm system may operate separately to the gas sensors which sense pH levels and CO₂ levels changing. The link between PAs and pH homeostatic
imbalances caused by respiratory abnormalities such as hyperventilation in PD patients forms the basis of the SFA theory of spontaneous panic, where CO₂ hypersensitivity may exist due to the abnormal suffocation alarm monitor (Vollmer, Strawn & Sah, 2015). Vollmer et al. (2015) propose a cycle of panic that explains both cued (expected) and spontaneous (unexpected) PAs, whereby cued PAs are a result of exteroceptive stimuli, and spontaneous PAs may be triggered by interoceptive sensory stimuli (see Figure 2).

Figure 2. Pathogenesis of panic attacks in panic disorder (adapted from Vollmer et al. 2015).

When arterial CO₂ is raised, brain arterioles dilate and blood flow increases. On the contrary, when arterial CO₂ is lowered, vasoconstriction occurs and cerebral blood flow decreases. Vasodilatory alterations caused by arterial CO₂ may be
mediated by changes in extracellular pH and local variations in the concentrations of Potassium (K+) and adenosine may also play a key part (Kandel et al., 2013). Several studies have suggested a dysregulation of respiratory physiology in patients with PD (Abelson, Weg, Nesse & Curtis, 2001; Gorman, Fyer & Goetz, 1988; Wilhelm, Trabert & Roth, 2001).

Potassium (K+) is imperative for the homeostasis of the human organism. Life threatening cardiac arrhythmias can be caused by the disruption of normal electrical excitability caused by K+ falling or rising, and the cell membranes becoming hyperpolarised or hypopolarised (McDonough & Youn, 2017). K+ channels are crucial in both excitable and non-excitable cells for the regulation of cell volume, membrane potential, secretion of salt, hormones, and neurotransmitters (Schwartz & Bauer, 2004). Multiple renal and extrarenal mechanisms regulate the K+ homeostasis within very tight parameters. Evidence suggests that acute challenges such as hypercapnia and hypoxia are both detected through tandem acid sensitive potassium channels which are located at carotid body chemoreceptor cells and plays a central role in peripheral chemosensitivity (Trapp et al., 2008).

A recent meta-analysis (Grassi et al., 2014) demonstrated baseline respiratory abnormalities in participants with PD compared to participants without PD. Participants with PD in this study differed to participants in the social phobia and generalised anxiety disorder group when compared, as the PD group demonstrated a lower end-tidal CO₂ pressure and a higher mean respiration rate at baseline. Differences were also noted in venous CO₂ pressure which was lower in the PD group and in the bicarbonate ion concentrations which were higher in the PD group. It was
concluded that these unique baseline respiratory abnormalities and the chronic hyperventilation may be specific to PD pathophysiology as opposed to other anxiety disorders. These findings are consistent with previous research (Colasanti et al., 2008; Ramirez, 2014; Sikter, Frecska & Braun, 2007).

PD patients commonly report respiratory abnormalities. Chronic obstructive pulmonary disease (COPD) has received the most attention (Kunik et al., 2005). COPD is a severe lung disease which is characterised by airway restriction and subsequent limitation of airflow and often presents with chronic bronchitis and/or emphysema (Barrera, Grubbs, Kunik & Teng, 2014). Several studies have examined the comorbidity of depression and anxiety symptomatology in COPD patients in a number of pulmonary clinics as assessed by various self-report anxiety and depression measures (Kunik et al., 2005). The prevalence of comorbid depression and anxiety was increased in COPD patients (Bratek, Zawada, Barczyk, Sozanska & Krysta, 2013; Bratek et al., 2015) and in their spouses too (Kuhl, Schurmann & Rief, 2008). Yohannes, Baldwin, and Connolly (2000), found that 37% of primary care outpatients with COPD who had depressive symptoms also had anxiety symptoms.

Indeed respiratory disorders including (COPD) and asthma among patients suffering from PD have a lifetime prevalence that is estimated to be 47% (Barrera et al., 2014). There have also been reports of high comorbidity between PD and respiratory abnormalities, which suggests that respiratory dysfunction plays a central role in PD (Simon & Fischman, 2005). Furthermore, research implicates that there may be a familial link between COPD and PD (van Beek, Schruers, & Griez, 2005).
Hyperventilation has numerous empirical and theoretical associations to anxiety and panic. Low CO₂ levels can develop quite quickly even in the absence of functional breathing disorders and this is because of the very high solubility of CO₂ which is twenty times more soluble than O₂ (Davies & Moore, 2003). Hyperventilation can easily result from non-metabolic stimuli, including stress, anxiety, or increased sensations of dyspnea, which in turn depletes CO₂ and resultant hypocapnia (Gotoh et al., 1965; Wilhelm, Gerlach & Roth, 2001). The effects of hyperventilation and depletion of CO₂ are pronounced and include increased neuronal excitability and reduced cerebral blood flow (Papp, Klein & Gorman, 1993). It is well understood that symptoms such as numbness, tingling sensations, dizziness, and muscle hypertonicity could result from hyperventilation. These symptoms could be attributed to hypocapnia and respiratory alkalosis, in which the body fluids have too much base and too little acid, resulting from an increased gas exchange in the lungs (Courtney, 2009). Intracellular pH (pHi) and cellular metabolism are impaired, as well as the regulation of cerebrospinal fluid pressure (Freire & Nardi, 2012).

Hypocapnia produces bronchoconstriction in the lungs and vasoconstriction in the blood vessels (Freire & Nardi, 2012). The depleted levels of CO₂ cause alkalosis, leading commonly to a reduction of cerebral oxygen metabolism, due to the Bohr effect (Fried, 1987). Relative to the Bohr effect, the affinity of haemoglobin towards oxygen is reduced and favours the oxyhaemoglobin dissociation when PaCO₂ increases (Kandel et al., 2013). The oxyhaemoglobin dissociation curve has a strong affinity to O₂ so it ensures a stable oxygen delivery to the viscera, even under difficult conditions (i.e., when engaging in strenuous physical activity) (Wilhelm, Gevirtz & Roth, 2001). Adverse effects of hypocapnia can also result in reductions in blood pressure, myocardial contractility, cardiac blood flow, and alterations in pH regulation.
and electrolyte balance. Given the widespread physiological effects of hypocapnia and the consequences of respiratory alkalosis, it is not surprising that breathing dysfunction has been associated with hyperventilation syndrome (Courtney, 2009) and that hyperventilation theories have been used to explain panic.

In the general population the prevalence rate of dysfunctional breathing characterised as breathing too fast and shallow has been as high as 5-11% (Fried, 1987; Hornsveld & Garrsen, 1997; Lum, 1981). In asthma sufferers, it is as high as 30% (Thomas, McKinly, Freeman & Froy, 2001) and in anxiety sufferers as high as 83% (Cowley & Roy-Burke, 1987). Consistent with previous findings, Freire et al. (2013) reported the respiratory subtype correlated with high CO₂ sensitivity (Biber & Alkin, 1999; Nardi et al., 2006; Valenca, Nardi, Nascimento, Zin & Versiani, 2002).

1.2.2.6 Neuroanatomical Theories

Neuroimaging studies have been fruitful in demonstrating that anxiety disorders such as PD which involve the fear circuitry, support the Deakin–Graeff hypothesis which proposes that PD is characterised by underactivity in the prefrontal cortex (PFC), which in turn decreases the amygdala inhibition (Deakin Graeff, 1991; Berkowitz et al., 2007). Optogenetic and chemogenetic methods have been used in animal models to study fear circuits involved in normal panic/fear as well as pathological panic/fear (Pare & Quirk, 2017), however, the neural pathways involved in initiating PAs in humans still remain poorly understood (Wiest, Lehner-Baumgartner, & Baumgartner, 2006).
Currently, a combination of complex fear circuitry and anxiety circuitry are implicated in the functional aetiology of PD (Tovote, Fadok & Luthi, 2015). When an individual perceives a stimulus as potentially threatening, a combination of adaptive changes involving neurochemical, neuroendocrine and behavioural responses are activated in an effort to maximise chances of survival. These neurobiological fear responses comprise the fear circuitry and include the amygdala, thalamus, hippocampus, insula and prefrontal cortex (Dias & Thuret, 2016).

The neuroanatomical theory of PD was first proposed by Gorman et al. (1989). It was suggested that the dysfunctional integration of information and subsequent discoordination of cortical and subcortical neural circuitry is involved in PD. Gorman et al. (1989), initially proposed that PAs are resultant from increased activity of the noradrenergic neurons of the locus coeruleus (LC), a nucleus in the pons of the brainstem responsible for physiological responses to stress and panic. Furthermore, it was suggested that anticipatory anxiety involves the limbic structures and that the prefrontal cortex (PFC) is responsible for phobic avoidance (Canteras & Graeff, 2014). Based on this theory, Gorman and his colleagues hypothesised that psychopharmacological interventions such as selective serotonin reuptake inhibitors (SSRIs) may reduce PAs by decreasing the amygdala activity and by inhibiting projections to subcortical sites including brainstem (Gorman et al., 2000). Furthermore, Gorman et al. (2000) suggested that psychotherapies including CBT, most likely act on the hippocampus by deconditioning contextual fear, decreasing cognitive misappraisals, and disproportionate emotional reactions by reinforcing and strengthening the ability of the medial PFC to inhibit the amygdala (Gorman et al., 2000).
In Gorman’s revised hypothesis, neuroanatomical pathways were identified and mapped in humans, based on similarities between conditioned fear responses in animals and PAs in humans (Le Doux, Cicchetti, Xagoraris & Romanski, 1990). In an attempt to explain panic and examine the fear circuits involved in the brain, several neuroanatomical models have been proposed. It has been proposed that hypersensitivity in the brainstem and the amygdala play a role in the pathogenesis of PD (Gorman et al., 2000). Sub-cortical and cortical regions such as the amygdala, thalamus, hypothalamus, insula cortex, and prefrontal cortex, are involved in the fear network, which is predicted to be activated transiently in PD thus suggesting that PD is best considered as a systems level abnormality.

The amygdala plays a significant role in the formation of memories as well as in the elicitation of strong emotional responses (Kim & Jung, 2006; Maren, 2008; Ziemann et al., 2009). Research conducted over the last several decades has revealed that the amygdala is an important brain structure that is essential for learned and innate fear and its function is pivotal to learning the association between conditioned and unconditioned, aversive, fear-evoking stimuli (Kim & Jung, 2006; Maren, 2008; Ziemann et al., 2008). The processing and directing of the inputs and outputs of fear behaviours occur at the amygdala and therefore it is a key structure to fear behaviours (Ziemann et al., 2008). It is well known that the amygdala incorporates sensory inputs received from various brain structures in producing physiological and behavioural expressions of fear (Wemmie, 2011; Ziemann et al., 2008). Whilst Gorman’s panic amygdala model has gained popularity, it was discredited by studies that found that patients suffering from the rare autosomal recessive Urbach–Wiethe disease, who are lacking an amygdala, develop PAs spontaneously and in response to
the 35% CO$_2$ challenge (Feinstein et al., 2013). This has contradicted previous findings that the amygdala is a key region in the initiation of panic attacks (PAs). Similarly, Wiest, Lehner-Baumgartner, Baumgartner, (2006) in their study reported a case study of a patient with bilateral selective lesions of the amygdala, experiencing PAs, suggesting that the initial pathology is not necessarily restricted to fear circuits such as the amygdala. However, in support of the role of the amygdala in fear processing, there have been studies which have found that the amygdala in humans with bilateral damage has notably impaired the processing of fearful facial expressions (Adolphs, Tranel, Damasio & Damasio, 1995; Le Doux et al., 1990).

Deep brain stimulation studies have shed some light in deepening our understanding of which areas are implicated in the induction of PAs and fear responses (Rasche et al., 2006; Wilent et al., 2011). Meletti et al. (2006) in their study, using intracerebral stimulation to stimulate the amygdala of 74 patients found that 85% of the emotions elicited that were observed were associated with fear, whilst 11% were associated with pleasant-happy feelings and 4% elicited a sad response. Their findings implicated that the medial temporal lobe structures are involved in fear expression. Moreover, Meletti et al. (2003) in their study found that unilateral damage in the amygdala can cause impairment in the recognition of facial expressions. In brain stimulation studies involving humans, stimulating the tuberal region of the hypothalamus (ventromedial/perifornical) region (Rasche et al., 2006; Wilent et al., 2010, 2011) or the dorsal periaqueductal gray regions (DPAG) (Nashold et al., 1969; Young, 1989) consistently elicits self-reports of dying, PAs, and anxiety accompanied by autonomic symptoms associated with PAs. Similarly in rats stimulation of the DPAG and hypothalamus evokes strong flight responses,
autonomic responses and aversive anxiety associated behaviours in rats (Shekhar, 1993; Shekhar, Hingtgen & DiMicco, 1990; Shekhar, Keim, Simon & McBride, 1996; Schenberg, 2010; Schenberg, Costa, Borges & Castro, 1990). The circa strike defence which is activated by prominent sympathetic nervous system arousal and active defensive behaviour also implicates the DPAG (Hamm et al., 2016; Le Doux, 2012). A number of sites involved in the fear circuitry, including the prefrontal cortex, insula, thalamus, septohippocampal system, as well as LC and RN have also been implicated in the regulation of panic responses.

A regulatory dysfunction at any of the abovementioned key sites in this fear network may lead to the development of PD symptoms (Dias & Thuret, 2016). Furthermore, it has been found that different subsets of neurons in the dorsal raphe nuclei (DRN) are activated by anxiety and panic, respectively and therefore it is also implicated in the fear circuitry (Canteras & Graeff, 2014; Paul & Lowry, 2013; Spiacci et al., 2012). According to Shekhar et al. (1999) amongst the critical regulatory sites that elicit “panic-like” responses and are characterised by chronic GABA dysfunction, is the dorsomedial hypothalamus and the anterior basolateral amygdala which evoke physiological symptoms, and behavioural responses associated with PAs resultant from the blockade of GABA receptors.

1.2.3 Summary

The biological theories have provided sound insights into understanding the pathophysiology and aetiology of PD. Whilst biological theories have informed psychopharmacological treatments that have been successful in treating PAs (Bonn et al., 1984; Sheehan, 1982b), they have been limited in terms of their utility in the
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development of treatments outside of psychopharmacology. Several biological theories have been proposed to explain the aetiology of PD including metabolic, hormone, genetic, neurochemical and respiratory and hyperventilation theories.

Amongst the most popular are the neuroanatomical theories. Several brain regions have been implicated to be involved in the fear circuitry and include the amygdala, thalamus, hippocampus, insula and prefrontal cortex (Dias & Thuret, 2016). Numerous studies from clinical, provocation, neuroimaging, psychophysiological and translational models of animal research in relation to PD have contributed to our understanding and current knowledge of the fear circuitry in the brain and the relevance of critical neuroanatomical sites involved in PD (Gorman, Kent, Sullivan & Coplan, 2000; Gorman, Liebowitz, Fyer, & Stein, 1989; Klein, 1993; Ley, 1985; Perna, Caldirola, & Bellodi, 2004; Perna et al., 2014). However, despite having a greater understanding about individual structures that are involved in the pathophysiology of PD, much has yet to be determined about the functional connectivity of the relevant structures involved in the fear circuitry and we are far from having a satisfactory explanation of the causes and mechanisms of PD (Canteras & Graeff, 2014; Dias & Thuret, 2016). Hence, more sophisticated translational models are called for to determine what animal research is of empirical value to humans and to further understand the molecular and neural systems involved in PD. Moreover, with recent technological advances in neuroimaging techniques, more human research needs to be carried out, to establish underpinnings and new insights on the fear circuitry involved in PD and the variations between PD and other anxiety disorders. These findings may in turn help to inform new treatments for PD patients,
with the aim of restoring homeostatic parameters that have been compromised via the activation of the brain’s fear circuitry.

Psychological theories have also been prominent. In terms of efficacy, cognitive theories have gained increased acceptance as being superior in the treatment and management of PD and have informed the development of psychologically-based treatments, particularly cognitive behavioural therapy, (CBT) (Clark et al., 1985; Salkovskis et al., 1986a). An individual’s susceptibility to developing PD is influenced by a number of biological and psychological factors that create vulnerabilities. Additionally, the catastrophic misinterpretation of somatic sensations plays a key role in the maintenance of PD. Cognitive behavioural therapy and biological approaches focusing on an interaction of physiological and psychological factors are more likely to be equipped at integrating the relevant research findings that complement the development of more efficacious treatments for PD.

Further understanding of the complex biological basis of PD needs to be supported by scientific insights not solely concerned with biological factors of PD but also genetic and epigenetic factors related to neurochemical, respiratory, endocrine, cognitive and behavioural systems. A multifactorial approach and model for PD may also help inform the development of novel treatments and combined interventions targeting physiological, cognitive, and behavioural symptoms of anxiety and panic.
1.3 PHYSIOLOGY OF PANIC

The human nervous system is made up of two anatomically separate systems: the central nervous system (CNS) and the peripheral nervous system. Essentially, the peripheral nervous system comprises twelve pairs of cranial nerves and thirty-one pairs of spinal nerves, and their associated ganglia (Wood, 2012). The peripheral nervous system is further divided into two main parts: an afferent (sensory) division which transmits signals towards the CNS and an efferent (motor) division which transmits signals away from the CNS. The efferent division can be further subdivided into the somatic motor division which controls skeletal muscle and the visceral motor division which is also referred to as the Autonomic Nervous System (ANS) (Wood, 2012). The vagal nerve which is the longest nerve in the body plays a key part in the brain and viscera interplay within the ANS, as it is responsible for numerous homeostatic regulations of visceral functions (Bonaz, Sinniger, & Pellissier, 2016).

The ANS is responsible for our basic life support systems that occur without our conscious control. The ANS is involved in the unconscious regulation of visceral functions and coordinates cardiovascular, respiratory, digestive, urinary and reproductive functions without instructions or interference from the conscious mind (Martini, Nath & Bartholomew, 2012). The ANS comprises sympathetic and parasympathetic divisions. Parasympathetic activation conserves energy and promotes a state of “rest and digest” as seen indigestion. The overall pattern of parasympathetic nervous system (PNS) responses incorporate a decreased metabolic rate, heart rate and blood pressure, increased secretion by salivary and digestive glands, increased motility and blood flow in the digestive tract and stimulation of urination and defecation (Martini et al., 2012).
The sympathetic nervous system (SNS) is activated only during exertion, stress or emergency, whilst the PNS predominates during resting conditions. The SNS prepares the body for heightened activity and produces what is known as the autonomic fight or flight response. More recently, the freeze response has also been added to the fight or flight response and this is frequently observed when someone becomes so overwhelmed by their fear and anxiety that they freeze and become immobilised to act (Rothschild, 2017). In summary, the SNS activation is characterised by heightened mental alertness, increased respiration and metabolic rate, increased heart rate and blood pressure, activation of sweat glands, and reduced urinary and digestive functions. When sympathetic activation occurs, which is what happens during a panic attack (PA), an individual undergoes a number of physiological changes designed to prepare them to cope with a stressful situation. While the various symptoms of a PA may cause the person to feel that their body is failing, it is, in fact, protecting itself from harm.

From a physiological perspective, the various symptoms of a PA can be described as follows. Commonly PAs are characterised by a sudden onset of fear, where there is little provoking stimulus. This is followed by a release of adrenaline (epinephrine) and activation of the fight, flight or freeze response, which essentially prepares one’s body for strenuous physical activity. Tachycardia and hyperventilation are frequently reported to occur in PAs (Ley, 1992). Hyperventilation during a PA, which may be a direct response to sympathetic activation or triggered by a subjective difficulty in breathing results in a drop in carbon dioxide (CO₂) levels in the lungs and blood (Barlow, 2014). This, in turn, leads to changes in the blood pH levels (respiratory alkalosis or hypocapnia) which can trigger various symptoms including
numbness, tingling, dizziness and light headedness. The latter two of these symptoms are also caused by vasoconstriction which results from the release of adrenaline during a PA.

1.4 TREATMENTS OF PANIC DISORDER

Panic Disorder (PD) has been largely treated by psychopharmacological interventions and cognitive behavioural therapy (CBT) alone or in conjunction. Prior to 1980, biological theories dominated explanations regarding the aetiology and treatment of PD. Since 1980, psychological explanations and theories including conditioning and cognitive models have been developed to define PD and make its treatments more efficacious (Sanchez-Meca, Rosa-Alcazar, Marin-Martinez, & Gomez-Conesa, 2010).

According to Barlow, Allen and Choate (2016), while pharmacological and psychological approaches have been shown to be equally effective treatments, evidence implies that psychological treatments are more enduring after treatment discontinuation. Research suggests that CBT or pharmacotherapy should be the preferred strategy for treatment for PD (Chen & Tsai, 2016). Given that PD has demonstrated to have more of a chronic phenomenological nature, combined treatments are often more efficacious, Van Balkom et al. (1997), endorsed the combination of in vivo exposure and antidepressant medication for the treatment of PD, based on a meta-analysis of 106 studies. Bakker, van Balkom, Spinhoven, Blaauw and van Dyck (1998) a year later published a review of 68 studies which comprised an analysis of the long–term outcome of treatment. The researchers concluded that the superiority of the combination of antidepressants and exposure
therapy found earlier in Van Balkom et al. (1997), was confirmed at follow up. Furukawa et al. (2007), in their Cochrane review, demonstrated that there was sustained advantage for 6 to 24 months when psychotherapy and antidepressant medication is combined over an antidepressant alone. This led them to conclude that as a first line treatment combined therapy or psychotherapy alone should be recommended. Benzodiazepines are not usually recommended in combination with CBT as they are known to blunt the CBT treatment response (Watanabe, Churchill, & Furukawa, 2007).

Chen and Tsai (2016) maintained that first line treatment should be CBT and that the combination of CBT and pharmacotherapy should only be the second-line treatment strategy for treatment-resistant PD. Individual characteristics of patients with PD should be taken into consideration when choosing the most optimal treatment strategy. For instance, patients that are unable to tolerate the side effects of medication may benefit from CBT while pharmacotherapy may be more suited for those experiencing more physical symptoms of PD rather than cognitive symptoms (Chen & Tsai, 2016; Kircanski et al., 2009; Pattyn et al., 2015; Roshanaei-Moghaddam et al., 2011; Roberson-Nay et al., 2012; Western & Morrison, 2001). Patients with PD who possess effective self-control skills respond more successfully to treatments using CBT (Chen & Tsai, 2016; Dusseldorp et al., 2007).

Besides increasing self-efficacy and decreasing AS, increasing patients’ sense of controllability and predictability of events in one’s environment, and decreasing avoidance and neurotic self-preoccupation are key mindsets that need to be developed (Barlow, Allen & Choate, 2016). According to modern learning theory, anxiety too
can become a conditioned stimulus, thus leading anxiety to initiate panic (Barlow, Allen & Choate, 2016). Several treatment studies have also shown that behavioural therapy which involves extensive exposure therapy in both the short term and the long term, may be equally as effective as cognitive therapy in reducing PD (Margraf & Schneider, 1995; Telch, 1995).

The efficacy of the treatment of PD has been well established in the literature (Sanchez-Meca et al., 2010). In a meta-analysis of 65 studies between 1980 and 2006, 42 supported that when exposure therapy, relaxation training, and breathing retraining are combined, it gave the most consistent evidence for treating PD (Sanchez-Meca et al., 2010). Two treatments which have gained much attention that fall under the CBT model include Barlow and his colleagues’ panic control treatment (Barlow & Craske, 1989; Craske & Barlow, 2006) and cognitive therapy developed by Clark and Salkovskis (Clark, 1997; Clark & Salkovskis, 1989).

In Barlow’s treatment model, exposure of the patient to interoceptive sensations plays a key part. Feared sensations are elicited via exercises such as visualisation of anxiety provoking scenes, over breathing and spinning (Barlow, 2014). Psychoeducation of panic and the factors that may affect its origin and recurrence are further an important part of this treatment. Cognitive therapy is also included in the treatment which focuses on modifying catastrophic misinterpretations about panic and anxiety. Erroneous beliefs that overestimate the threat and danger that the PAs represent are addressed. The program incorporates progressive muscle relaxation which involves gradually tensing and relaxing various muscle groups paying particular attention to the bodily sensations and inducing relaxation and
warmth. Homework exercises are assigned to encourage client participation between sessions (Sanchez-Meca et al., 2010).

The cognitive therapy developed by Clark and colleagues includes both an educational and a cognitive component. The educational component focuses on briefing the client on the causes and triggers of PAs. The cognitive component focuses on identifying and challenging erroneous interpretations of the symptoms. The program includes breathing retraining to correct abnormal habitual breathing patterns such as hyperventilation, in order to alleviate fearful sensations. Furthermore, behavioural experiments are implemented in order to expose the client to their feared panic sensations and to encourage them to give up their safety behaviours. When comparing the two approaches, Barlow’s approach is characterised by an emphasis on exposing the clients to their interoceptive sensations whereas Clark’s approach focuses more on the cognitive component (Sanchez-Meca et al., 2010). Other treatment modalities have been applied in treating PD with some of the more common ones being, eye movement desensitization and reprocessing (EMDR) (Feske & Goldstein, 1997; Goldstein, de Beurs, Chambless & Wilson, 2000), psychodynamic therapy (Milrod et al., 2007), emotion regulation therapy (Shear, Houck, Greeno & Masters, 2001), breathing retraining (Meuret, Wilhelm, Ritz & Roth, 2008), gestalt therapy (Chambless, Goldstein, Gallagher & Bright, 1986), virtual reality exposure (Powers & Emmelkamp, 2008) and mindfulness based approaches (Roemer & Orsillo, 2005) including acceptance and commitment therapy (Forman et al., 2007).
According to Cosci (2012), promoting recovery early in the treatment process is seminal, given that PD often involves a staging process, implicating that the disorder may worsen over time if left untreated. Fava and Mangelli (1999) proposed a 4-stage model to describe the development of PD and agoraphobia. The first stage is characterised by the interplay of several predisposing factors including genetic vulnerability, personality features, anxiety sensitivity, health anxiety, and impaired psychological well being. Stage 2 involves the onset of agoraphobia, whereby Stage 3 involves the acute phase of PD. Stage 4 is represented by a chronic phase of PD, in which agoraphobia becomes more severe, and the risk of major depression is increased. Support for the staging model of PD and agoraphobia has been implicated by its utility to recognise PD early enough to be able to treat it successfully (McGorry 2007; McGorry et al., 2007). The model may also be able to assist with the development of therapeutic strategies for patients that are treatment resistant (Cosci, 2012).

The next section of the thesis will specifically explore cognitive behavioural therapy (CBT), acceptance and commitment therapy (ACT), in vivo exposure with the use of virtual reality, psychodynamic breathing retraining interventions and psychopharmacological treatments, as these appear to be most frequently used in the treatment of PD.

1.4.1 Cognitive Behavioural Therapy (CBT)

CBT for PD promotes the development of self-efficacy in which patients develop their belief and confidence that they are capable of effectively coping with panic-related symptoms. The role of the therapist in this process is to effectively
discuss the true dangers of panic symptoms and encourage client’s ability to manage
with their symptoms of panic (Casey, Oei & Newcombe, 2004; Gallagher et al.,
2013). Studies conducted have revealed that severity of PD symptoms can be
predicted based on the self-efficacy beliefs of patients (Gallagher et al., 2013;
Richards, Richardson & Pier, 2002; Telch, Brouillard, Telch, Agras & Taylor, 1989).
According to Fentz et al. (2014), panic self-efficacy plays a vital role in determining
the outcome of treatment for PD. Research shows that misinterpretations of bodily
sensations experienced during PAs as well as lack of self-efficacy in managing and
dealing with PAs are significant factors that influence resistance to treatment for PD
(Fentz et al., 2013, 2014; Gallagher et al., 2013; Hoffart et al., 2016; Noda et al.,
2007; Teachman et al., 2010).

Hoffart et al. (2016) in their study found that catastrophic beliefs are a
mediating factor contributing to either remission or persistence of PD. Decreasing
catastrophic misinterpretations of bodily sensations using CBT has been demonstrated
to lead to an overall reduction in symptoms (Teachman et al., 2010). According to
Gallagher et al. (2013), the greatest changes occurring early in treatment was in AS,
while self-efficacy experienced notable changes towards the end of treatment.

CBT has demonstrated the greatest effect on AS which impacts changes in
panic symptoms early in the treatment process. The focus of therapy revolves around
providing psychoeducation, breathing retraining and cognitive restructuring which in
turn impacts subsequent panic symptom changes (Gallagher et al., 2013). Effective
and fast improvements have been observed in relation to patients’ fear of bodily
sensations using CBT for PD (Gallagher et al., 2013).
Delivering psychoeducation about anxiety-related bodily sensations, developing interoceptive distress tolerance, in vivo exposures exercises, and restructuring of catastrophic appraisals of anxiety-related bodily sensations and cognitions, all part of CBT for PD, have been shown to decrease AS in patients with PD (Barlow, 1988, 2002; Craske & Barlow, 2013; Gallagher et al., 2013).

CBT is considered to be the preferred psychological treatment, given that is the most researched form of psychological therapy. Moreover, no other psychotherapies have systematically demonstrated that they are superior to CBT (David, Cristea & Hofmann, 2018). The efficacy of CBT as a treatment for PD has been demonstrated through large randomised controlled trials depicting evidence that treatment effects of CBT are larger than that of placebo as CBT has greater durability as well as producing similar outcomes to medication at post-treatment (Barlow, Gorman, Shear & Woods, 2000; Gallagher et al., 2013). Meta-analyses conducted (Mitte, 2005; Westen & Morrison, 2001) to date show that CBT has large effects on PD (Gallagher et al., 2013). This has also been evidenced by studies without a control condition, where patients despite being on a therapeutic dose of medication, demonstrated improvement following the introduction of CBT (Heldt, et al, 2003; Pollack et al., 1994).

Gallagher et al. (2013), emphasised the importance of correcting the maladaptive perceptions of bodily sensations that patients have early in treatment to facilitate positive outcomes. Increasing patients’ sense of mastery, self-efficacy and personal agency in their ability to cope with the disorder has been demonstrated by patients achieving an enhanced recovery. Evidence-based treatments are pointing to
the constructs of self-efficacy and anxiety sensitivity (AS) as playing a key part in the mechanisms of change of CBT for PD (Bouchard et al., 2007; Casey et al., 2005; Gallagher et al., 2013; Reilly et al., 2005; Shear et al., 2001; Smits et al., 2004). Research has demonstrated CBT’s efficacy in decreasing AS (Gallagher et al., 2013; Shear, Houck, Greeno, & Masters, 2001; Smits, Berry, Tart, & Powers, 2008). The importance of CBT’s efficacy in counteracting AS erroneous beliefs around is further supported by evidence that AS has demonstrated to directly impact other anxiety-related symptoms experienced by patients (Gallagher et al., 2013; Reilly, Gill, Dattilio & Mc Cormick, 2005; Smits, Powers, Cho & Telch, 2004).

In summary, CBT approaches focus on directly changing the form, frequency or validity of the context and function of psychological phenomena that includes feelings, sensations and thoughts. ACT, on the other hand, emphasises these as the target of change interventions (Blackedge, Ciarrochi & Deane, 2009; Hayes, 2004; Hayes, Villatte, Levin & Hildebrandt, 2011; Swain, Hancock, Hainsworth & Bowman, 2013).

1.4.1.1 Acceptance and Commitment Therapy (ACT)

According to Forman et al. (2007) amongst the new CBT approaches, ACT has been the most well researched. There is expanding evidence as demonstrated by meta-analysis, for the efficacy of ACT and anxiety disorders (Hayes, Luoma, Bond, Masuda & Lillis, 2006). The main aim of ACT is to assist clients in developing psychological flexibility for the purposes of adapting to novel potentially threatening contexts. This is achieved through six core therapeutic processes that include acceptance, cognitive defusion, mindfulness, values and committed action, and self-
as-context (Hayes et al., 2006; Luoma et al., 2007; Swain et al., 2013). ACT postulates that in order for clinical improvement to occur, patients are trained to feel bodily sensations and emotions, without active avoidance or suppression, as well as to focus on behaviour change in valued directions (Levitt et al., 2004). ACT aims to increase willingness and behaviour control while reducing experiential avoidance and attempts at internal control as it is believed that attempts at internal control and regulating internal experiences may be the problem and not the solution to the problem (Levitt et al., 2004).

Arch et al. (2009) conducted a study comparing 12 sessions of ACT to CBT with 36 participants diagnosed with PD/agoraphobia, social anxiety disorder (SAD) or specific phobia (SP). Results revealed that patients in the ACT group showed significant decreases in clinician and self-report measures, with both ACT and CBT showing similar reductions in clinician measures from moderate severity to subclinical severity post-therapy (Arch et al., 2009). In another study by Arch et al. (2012) comparing ACT and CBT in 128 participants with PD and/or agoraphobia, obsessive-compulsive disorder, generalised anxiety disorder (GAD), SAD, SP, found that both treatments produced equivalent reductions on both self-rated anxiety measures and clinician rated anxiety measures. Results revealed that patients in the ACT group showed significant decreases in clinician and self-report measures, with both ACT and CBT producing equivalent and reliable change in clinician measures from moderate severity to subclinical severity post-therapy (Arch et al., 2009). Furthermore results revealed ACT was more effective than CBT based on clinician-rated outcomes (Arch et al., 2012; Swain et al., 2013).
Feldner et al. (2003), in their study, were the first to demonstrate that experiential avoidance and emotion regulation strategies potentiate induced acute emotional distress using inhalations of 20% CO2-enriched air which are typically panicogenic under experimental conditions. Notably, such effects were largely providing evidence that experiential avoidance, but not other psychological risk factors for panic (e.g., anxiety sensitivity), tends to covary with a more exaggerated panic response, even in non-panic counterparts (Karekla, Forsyth & Kelly, 2004). Following several trials of CO2 inhalations, individuals high in experiential avoidance exhibited more panic symptoms, increased panic cognitions, fear, panic, and loss of control than their less avoidant counterparts (Forsyth, Barrios & Acheson, 2007).

Karekla (2004) in her dissertation study compared panic control treatment (PCT) with ACT enhanced CBT in 22 participants. Results revealed that participants in the PCT treatment group experienced more interference, agoraphobia severity and avoidance compared to the ACT enhanced CBT treatment group.

Meuret and colleagues (2012) investigated the effectiveness of ACT-enhanced exposure therapy for patients with PD with and without agoraphobia. Eleven participants were provided with 4 sessions of ACT with a focus on acceptance, defusion and value based behaviour which was followed by 6 sessions of exposure therapy adapted from the ACT theoretical model (Meuret et al., 2012). In the initial four sessions, participants reported significantly reduced agoraphobic cognitions, decreased AS and increased mindfulness. Out of 11 participants in this study, 8 completed treatment and reported at least a 30% decrease in severity of their PD (Bluett et al., 2014; Meuret et al., 2012).
Levitt et al. (2004) examined the effects of acceptance as opposed to suppression of emotions and thoughts during a 5.5% CO2 challenge in patients with PD. The research revealed that compared to patients in the suppression group, patients in the acceptance group reported less avoidance and subjective anxiety in a second challenge (Levitt et al., 2004). While participants did not report changes to experiencing panic sensations, their subjective anxiety and willingness to participate in another challenge did differ among all three groups (suppression group, acceptance group, and control group) (Levitt et al., 2004). The study also found that prior to a CO2 challenge, a 10-minute acceptance intervention assisted in reducing participants’ subjective anxiety and avoidance. In summary, the results of this study indicate that the two goals of acceptance based interventions were met, which include: (1) encouraging patients to fully experience emotions while remaining non-judgemental and (2) increasing willingness for participation in valued activities (Levitt et al., 2004).

In reviewing the studies many of them lacked randomised controlled studies and an active comparison group. Moreover, they did not compare ACT to standard cognitive therapy and upon additional investigation, most of these controlled studies which demonstrated efficacy in anxiety treatment were conducted by investigators with an allegiance to ACT (Forman et al., 2007). According to Powers et al. (2009), ACT did not outperform established treatments; hence, they concluded in their study that there was no distinct advantage of using ACT over existing established treatments.
Chapter 1.

Panic Disorder

1.4.1.2 In Vivo Exposure and Virtual Reality Exposure

In vivo exposure has been a traditional form of CBT that aims to reduce the fear associated with the interoceptive and exteroceptive triggers (Barlow & Craske, 2014). In a meta-analysis of studies investigating the efficacy of pharmacological and psychological interventions, results yielded support for the efficacy of cognitive therapy and or in vivo exposure therapy which involves gradually exposing the client to feared situations (Bakker, Balkom, Spinhoven, Blaauw & van Dyck, 1998; Chambless & Gillis, 1993; Clum, Clum & Surls, 1993; Cox, Endler, Lee & Swinson, 1992; Gould, Otto & Pollack, 1995; Mattick, Andrews, Hadzi-Pavlovic & Christensen, 1990; Mitte, 2005; Westen & Morrison, 2001). Meta-analyses that have addressed the differential efficacy of psychological and pharmacological treatments have revealed positive results for both of these treatments (Cox et al., 1992; Mitte, 2005; van Balkom et al., 1997; Wilkinson, Balestriere, Ruggeri & Bellantuono, 1991).

The use of virtual reality (VR) as a tool for providing exposure is a relatively recent development in the behavioural treatment of specific phobias (Powers & Emmelkamp, 2008). Clients are exposed to virtual stimuli instead of being confronted with real anxiety provoking stimuli (Powers & Emmelkamp, 2008). In order to immerse patients in the generated virtual environment, VR integrates visual displays, body tracking devices, real-time computer graphics, and other sensory input devices (Powers & Emmelkamp, 2008).

The use of VR in treating more complex anxiety disorders such as panic disorder with agoraphobia is scarce with only a few randomized control trials that have been conducted to date (Meyerbroker & Paul, 2010). Agoraphobic avoidance
behaviour and panic is the focus of treatment with particular emphasis on exposure to agoraphobic avoidance behaviour which comprises exposing patients to feared situations through virtual environments (Meyerbroker & Paul, 2010).

Choi et al. (2005) conducted a study comparing group experiential cognitive therapy including VR exposure therapy, to a panic control program. Patients received either twelve sessions of the panic control program (Craske & Barlow, 1994) or four sessions of experiential cognitive therapy which consisted of relaxation training, psychoeducation, VR exposure and interoceptive exposure). The study revealed that both treatments were equally effective immediately following its completion, however at six-months follow up, these results were not maintained with the panic control group showing higher end-state functioning compared to the experiential cognitive therapy group (Choi et al., 2005; Meyerbroker & Paul, 2010).

In a study by Botella et al. (2007), a comparison between nine treatment sessions of CBT with VR exposure therapy, nine sessions of CBT plus exposure in vivo and waiting list control condition was conducted. Results revealed that between the two treatments conditions, no differences in effectiveness were found as both were superior to the waiting list control. At 12-months post-treatment, results were maintained. Some limitations noted with VR exposure therapy including challenges with providing training for mental health providers in the use of VR exposure behaviour therapy, and the lack of a standardised procedure in the delivery of treatment (Botela et al., 2015).
Penate et al. (2008) conducted a study comparing VR exposure therapy to CBT in patients with PD. Eleven sessions of CBT or combined CBT and VR were provided to patients who in conjunction took antidepressant medication. Results demonstrated that both treatments were found to be effective at post-treatment. The same research team who conducted a study investigating CBT with exposure in vivo or a combination of CBT and VR exposure therapy for treating a diagnosis of PD and agoraphobia in 27 patients found no differences between the two treatments at post-treatment (Pitti et al., 2008). Results indicated that patients, however, favoured the combined treatment over CBT alone (Pitti et al., 2008). The sole use of VR exposure therapy in treating PD has not received much attention, with only Botella et al. (2007) comparing VR exposure therapy and exposure in vivo found both to be equally effective in treating PD (Meyerbroker & Paul, 2010).

The use of in vivo exposure and VR exposure are usually accompanied by other psychological treatments. Many of the psychological treatments that are widely used to treat PD encompass breathing training with an aim to mediate dysfunctional habitual breathing patterns and to improve anxiety and general health. Barlow et al. (1988) developed interoceptive exposure which was initially aimed at treating PD with agoraphobia, as it was recognized that the context of anxiety and fear experienced was external as well as internal (Barlow, 2016; Barlow, Allen & Choate, 2016). Pompoli et al. (2018) in their review postulated that CBT packages for PD including face-to-face and interoceptive exposure components demonstrated superiority over muscle relaxation and VR exposure components.
1.4.2 Psychodynamic Therapy

Psychodynamic therapies have also been used to treat or to conceptualise PD. Amongst the psychodynamic treatments that are specific to PD is the panic-focused psychodynamic psychotherapy. This treatment modality is based on the theoretical foundations that a PA can be understood as the consequence of intrapsychic conflict arisen from unconscious fantasies that clash. One study randomised 49 patients to either panic-focused psychodynamic psychotherapy or to an applied relaxation treatment was used to evaluate the efficacy of panic-focused psychodynamic psychotherapy (Milrod et al., 2007). Results demonstrated superior outcomes for the group receiving panic focused psychodynamic therapy, as they reported a significantly greater reduction in panic symptoms and higher than the group receiving applied relaxation. However, it is less than clear if the applied relaxation treatment actually was in accordance with the behavioural coping technique developed by Öst (1987).

1.4.3 Breathing Training

A range of conditions including asthma, heart disease, depressive disorders and anxiety are leaning towards breathing therapies given the growing body of scientific evidence supporting their efficacy. Buteyko breathing techniques which involve breath-holding in combination with reduced volume breathing have been researched extensively for the efficacy on asthma with there being at least five published clinical trials to date (Abramson et al., 2004; Bowler, Green & Mitchell, 1998; Cooper et al., 2003; Cowie, Underwood & Reader, 2008; McHugh, Aitcheson, Duncan & Houghton, 2003; Opat, Cohen & Bailey, 2000; Slader et al., 2006). In psychological conditions such as depression, stress and anxiety, breathing
biofeedback and yoga based breathing techniques have been found to be effective
(Han, Stegen, De Valack, Clement & Vande Woestjine, 1995; Janakiramaiah et al.,
1998; Karavidas et al., 2007; Meuret, Wilhelm, Ritz & Roth, 2008; Murthy,
Janakiramaiah, Gangadhar & Subakrishna, 1998; Tweedale, Rowbottom & McHardy,
1994). Research in the field of respiratory psychophysiology and claims posited by
several eastern philosophies and traditions support the idea that emotional states are
largely dependent on breathing patterns, and that altering one’s breathing pattern
voluntarily can alter one’s emotional state (Boiten, 1998; Boiten, Frijda & Wientjes,
1994; Brown & Gerbarg, 2005; Grossman, 1983; Ley, 1999: Tweeddale, Rowbottom
& McHardy, 1994; Van Diest, Thayer, Vandeputte, Van de Woestijne & Van den
Bergh, 2006; Blom et al, 2014).

For this reason, motivated by a biological basis for panic, breathing training is
another common intervention used in the treatment of PD (Barlow, 2014; Courtney,
2009; Meuret et al., 2003). Breathing training derives its therapeutic effect through
correction of deranged respiratory patterns (i.e., thoracic breathing, hyperventilation)
(Klein, 1993; Ley, 1985). Hypocapnia (lower than normal levels of carbon dioxide) is
thought to be the primary cause of panic (Ley, 1985) or the secondary cause of panic
(Klein, 1993). Unpleasant bodily sensations experienced as a result of hypocapnia
(i.e., dizziness, numbness, tingling) may precipitate panic (Carr, Lehrer & Hochron,
1992; Chambless, Caputo, Bright & Gallagher, 1984), and hypocapnia in itself can
occur as a result of mental illnesses or due to intacranial hypertension and
hyperkalaemia (Laffey & Kavanagh, 2002; Meuret, Rosenfield, Seidel, Bhaskara, &
Hoffman, 2010). Changes in panic symptoms can be achieved through
therapeutically increasing the partial pressure of carbon dioxide (PaCO₂) (Meuret et al., 2010).

1.4.3.1 Breathing Training Treatments

Capnometry-assisted respiratory training (CART) is a 4 week-training program developed to systematically alter hypocapnia in PD patients (Meuret et al., 2008). CART is an alternative breathing retraining method, as it assures the manipulation and assessment of respiratory physiology (Meuret et al., 2003). CART teaches patients to raise subnormal levels of PaCO₂ through immediate feedback of end-tidal PaCO₂ that is monitored through a portable capnometer, in order to increase patients’ control over dysfunctional gas exchange and the symptoms that develop because of that (e.g., dizziness, shortness of breath) (Meuret et al., 2010).

Meuret et al. (2008) conducted the first randomised controlled trial study comparing CART to waitlist for patients with PD with agoraphobia. Results demonstrated that 68% of patients achieved significant reductions in panic symptom severity at post-treatment and at 2 and 12 months follow-up, 79% and 93% of such patients showed significant reductions in severity of panic symptoms (Meuret et al., 2008). Results yielded that patients were able to achieve sustained normalised levels of PaCO₂.

For several decades, respiratory abnormalities have been postulated as significant factors in the development and maintenance of anxiety-related problems. Breathing training/retraining has become a major therapeutic strategy in the treatment of PD, often used as a component of a treatment package (Barlow & Craske, 1989;
Telch, Shermis & Lucas, 1989; Wilhelm & Margraf, 1997) or as the sole component of treatment (Clark, Salkovskis, & Chalkley, 1985; Han, Stegen, deValck, Clement, & Van deWoestijne, 1996; Hibbert & Chan, 1989; Rapee, 1985; Salkovskis, Jones & Clark, 1986). Breathing techniques are becoming increasingly popular given the impact of dysfunctional breathing in common conditions including asthma, cardiovascular disease, chronic pain, depression, anxiety and panic (Courtney, 2009).

In most panic treatment approaches, the reversal of the fight-or-flight response is achieved by breathing retraining, which involves practicing controlled slow breathing as well as various techniques which assist with relaxation, such as progressive muscle relaxation and visualisation. The rationale of breathing training is based on the hyperventilation theory of anxiety that supports a central role for hypocapnia in panic symptom reduction (Ley, 1985, 1992). The essential aim of these techniques is to terminate the positive feedback loop, the vicious panic cycle, by reducing the respiratory rate and thus increase PaCO₂ from hypocapnic to normal levels (Clark, 1986). Cognitive theorists would emphasise that breathing control techniques help clients learn to reinterpret somatic symptoms of hyperventilation as being a normal physiological reaction rather than life-threatening. Wolpe and Rowan (1988) assert that a feeling of immediate control over hyperventilation symptoms should generally hinder the experience of anxiety and in particular panic.

Voluntary hyperventilation (VH) has been used as an educational tool to simulate feared physical sensations and demonstrate the idea of the vicious cycle of panic. Voluntary hyperventilation tests have been applied in the laboratory to understand the physiological and psychological mechanisms involved that initiate and
maintain anxiety. Moreover, they have been applied therapeutically in the treatment of anxiety disorders. From the theoretical perspective of hyperventilation theories of anxiety, voluntary hyperventilation is useful diagnostically to the clinician and educationally to the patient. From the theoretical perspective of CBT, voluntary hyperventilation is an alternative method to induce panic like sensations and to activate catastrophic cognitions that need restructuring in PD patients (Barlow & Craske, 2014).

Chronic emotional stress and states of hyperarousal have been found to alter breathing patterns. Breathing irregularity is a common symptom in patients suffering PD and other anxiety disorders. Dysregulation of normal breathing patterns are observed and specific diaphragmatic changes are noted. Fluoroscopic studies demonstrated that the diaphragm becomes flat and is immobile in situations of emotional stress. When a fight or flight response is activated, fast shallow and thoracic breathing dominates. Increased levels of tonic contraction of respiratory muscles expend a lot of energy and homeostatic functions necessary for renewal and repair are compromised (Courtney, 2009). Controlled respiration aids the system to return to a physiological rest state and appears to regulate neurological function which assists with the decrease of SNS activity and increased PNS activity (Courtney, 2009). Frequent and prolonged practice of several breathing techniques combining slow diaphragmatic breathing, long breath retentions, alternate nostril breathing has been known to benefit by resetting the autonomic balance and amplifying PNS responses (Christoforidi et al., 2012; Mana, 2010; Pal, Velkumary, & Madanmohan, 2004).
Meuret et al. (2003) identified nine studies as using breathing training (BT) alone or in combination with other treatment modalities. The BT treatment took place over the course of 2-4 weeks and comprised one to five sessions. The findings of most of the nine studies revealed decreases in PA frequency, severity and self-reported anxiety. Although some of these studies suggest that BT is effective alone or in combination with other treatments, some studies suggest no greater efficacy compared to other alternative treatments. Moreover, a number of limitations in these studies do not warrant this to be a fruitful meta-analysis, including the extensive variation in patient selection, study design, underlying rationales and BT techniques used. Meuret et al. (2003) concluded that more studies are needed to test the efficacy of BT alone and that the techniques used should take into consideration respiration rate and tidal volume in the regulation of blood gases (PaCO₂).

To date, there have been a large number of breathing techniques that have been found to be effective in regulating mental and emotional states such as the Buteyko breathing techniques (Abramson et al., 2004) and the Wim Hof breathing method (Kox et al., 2014). The evidence for the ability of breathing therapies to correct breathing dysfunctions is relatively sparse as research has largely focused on psychological outcomes rather than examining the efficacy of breathing parameters. Furthermore, breathing retraining has yielded mixed results and is not as effective as CBT where the client is encouraged to stay with the sensations akin to “floating with panic” or “riding the wave” (Barlow & Craske, 2014). Despite a number of studies suggesting that breathing retraining is effective in reducing the frequency of panic attacks (PAs), concerns have been raised about its regular use. Taylor (2010) suggested that the routine use of breathing retraining may only be effective in patients
who hyperventilate or breathe via the chest. Another concern raised is that breathing retraining may prevent patients from learning that their catastrophic beliefs are irrational, hence being counterproductive (Barlow & Craske, 2014; Taylor, 2010).

1.4.4 Pharmacological Treatments

A number of pharmacologic agents have demonstrated efficacy in the treatment of PD. Selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, tricyclic and heterocyclic antidepressants, and monoamine oxidase inhibitors (MAOIs) are amongst the several classes of drugs that are used in the treatment of PD (Chen & Tsai, 2016). Nowadays antidepressants which act on aminergic symptoms are used more commonly to treat panic symptoms rather than benzodiazepines that potentiate the effect of GABA, which is the principal inhibitory neurotransmitter in the central nervous system (CNS) at various receptors (Taylor & Arnow, 1988). However, it is now widely accepted that, although medications working on the GABA receptors are highly effective, they come at a cost, as they are highly addictive and impact on cognitive functioning (Andrews, Corry, Oakley-Browne & Shepherd, 2003). Moreover, it is because of problems with side effects and safety concerns such as sedation, dependence and tolerance that the benzodiazepines have been contraindicated for long-term use (Baldwin et al., 2005; Bandelow et al., 2008; Garner et al., 2009; Johnson, Federici & Shekhar, 2014; Petersson, 1994).

Nevertheless, despite the side effects commonly experienced by patients, reports suggest that they are excellent anxiolytics and efficacious for the treatment of PD (Graeff et al., 2003; Marks et al., 1993; Risborough, 2009). A systematic review
and meta-analysis of 22 studies compared the efficacy of all the classes of antidepressants against benzodiazepines and yielded support that benzodiazepine trials were comparable or demonstrated greater improvements with fewer reported adverse effects in PD or GAD patients, compared with newer class antidepressants (Offidani, Guidi, Tomba & Fava, 2013). Some of the most common associated side effects with the newer class antidepressants (SSRIs and SNRIs) have included sexual dysfunction, weight gain and sleep disturbance (Ferguson, 2001; McHugh et al., 2009), which have resulted in high rates of treatment discontinuation (Cowley et al., 1997; Dewand & Anand, 1999) and greater attrition rates as compared to CBT in clinical trials (Butler et al., 2006).

Nardi et al. (2012) in a randomised controlled naturalistic 8-week study compared the safety and efficacy of treatment with clonazepam and paroxetine in PD patients with or without agoraphobia. They found that the benzodiazepine was superior to the antidepressant, as clonazepam resulted in fewer PAs at week 4 and overall greater clinical improvements at week 8. Moreover, patients treated with clonazepam reported fewer adverse symptoms than patients treated with paroxetine. (Nardi, Valenca & Freire et al., 2011; Nardi et al., 2012). Notwithstanding, these findings are compelling and have triggered some debate amongst the medical community concerning preferences for first-line treatments, and their efficacy for treating different anxiety disorders as well as relative adverse effects (Kaplan, 2013).

At present, SSRIs are typically, the preferred choice of psychotropic medication used to treat PD and remain to date the first-line recommended psychopharmacological treatment (Bandelow et al., 2008). Andrisano, Chiesa and
Serreti (2013), in their meta-analysis found that there is a close link between serotonin and PD and tryptophan depletion as evidenced by the increase of PAs and anxiety symptoms in PD. Furthermore, their meta-analysis demonstrated higher anti-panic efficacy in SSRI’s as compared to other medications. Burghhardt et al. (2007), in their study, found that rats that were treated acutely by SSRI injections including citalopram and fluoxetine demonstrated enhanced conditioned fear responses, providing support that SSRIs become effective only after 2-3 weeks, of repeated treatment. According to Klein (2013), serotonergic antidepressants are effective with spontaneous and situationally predisposed PAs. To date, the mechanisms involved in the therapeutic actions of the compounds in SSRIs remain largely unknown (Al-Damluji, 2004).

1.5 SUMMARY OF CHAPTER

Panic research needs to continue to build on existing theories and on well established evidence-based treatments and draw on advances in the disciplines of psychology, physiology, neuroscience and psychiatry to further our understanding of the complexities associated with panic and its pathophysiology. Amongst some of the treatments for PD that yield positive therapeutic outcomes, are CBT, ACT, breathing retraining, in vivo and virtual reality exposure, psychodynamic approaches and pharmacological therapies. Despite a lot of other treatment modalities gaining popularity, CBT appears to be the dominant modality of all the psychological interventions and the preferred choice for a first line treatment. It is well established that it is the gold standard treatment for PD in the literature and that a combination of pharmacotherapy and CBT might be more appropriate as a second line treatment (David, Cristea & Hofmann, 2018).
In primary care and community health settings, anxiety disorders are too often, not detected, or under recognised and hence not treated. Frequently, it is when a patient demonstrates significant distress or experiences complications from the disorder, that treatment is indicated. (Bandelow, Michaelis & Wedekind, 2017). Psychopharmacological and psychological treatments can sometimes be lengthy, with high drop-out rates and poor compliance (Ferguson, 2001). Hence there is a need for the development of treatments that are more simple, and practical and cost-effective, whereby treatment compliance and efficacy is improved.
Chapter 2

The Diving Response and its Applications

2.1 BREATH-HOLDING (APNEA)

Breath-holding and controlled slow breathing are commonly used in the treatment of panic both for exposure of interoceptive symptoms or sensations, and for the reversal and prevention of anxiety and panic symptoms (Barlow, 2017). Breath-hold (BH) training also known as apnea training has been used widely to enhance sports performance in athletes and to train the body to adapt to the scarcity of oxygen (Hutchinson, 2018). Cardiovascular adaptations such as the diving response (DR), are induced during apnea (i.e. cessation of breathing or cooling of the face) and are focused on reducing overall oxygen consumption (Breskovic et al., 1985; Guimard et al., 2014).

2.2 THE DIVING RESPONSE (DR)

The DR, exhibited by all air-breathing vertebrates is a physiological adaptation and reflex that optimises respiration, allowing humans to endure a lack of oxygen underwater and remain underwater for extended periods of time. Furthermore, this physiological response makes it possible for humans to dive to depths thought potentially fatal by the medical profession for the human body to survive. The current world record for breath-hold duration is 11.35 minutes and depth of 214 metres (Ostrowski et al., 2012).
For more than a century, the DR has been studied extensively in animals; however human studies are limited (Shamsuzzaaman et al., 2014). It is elicited by apnea (cessation of respiration) and stimulation of cold facial receptors (cold facial immersion) (Foster & Steel, 2005). The DR is the most powerful autonomic reflex characterised by bradycardia, peripheral vasoconstriction, blood centralization, decreased cardiac output, increased arterial blood pressure and decreased arterial oxygen saturation (SaO₂) (Alboni, Alboni, & Gianfranchi, 2011; Andersson & Schagatay, 1998; Foster & Sheel, 2005).

There are a number of factors that stimulate the DR, although the contributions of each in eliciting the DR and the central mechanisms that control and regulate these responses have not been fully determined (Baranova, Berlov & Yanvareva, 2016). Factors activating the DR include, apnea, also known as breath-holding (BH), cold facial immersion (CFI) and tactile stimulation of receptors of the face, hypercapnic and hypoxic factors influencing chemoreceptors on the vascular bed, carotid sinuses, medulla oblongata centres (i.e., respiratory, vasomotor) (Andersson, Liner, Runow & Schagatay, 2002; Baranova et al., 2016). Upon initiation of the DR, the physiological changes include: a decrease in heart rate (bradycardia) (Asmussen & Kristiansson, 1968); constriction of blood vessels in certain parts of the body (vascular constriction); reduced blood flow to peripheral capillary beds (Leuenberger, Hardy, Herr, Gray & L.I., 2001) increased blood pressure; and the spleen contracts to release more oxygen carrying red blood cells into bloodstream (Ferrigno et al., 1997). There is also increased output in the volume of blood being pumped out of the heart when the DR is activated (Ferrigno, Hickey, Liner, & Lundgren, 1986). Anatomic differences between humans and diving animals...
point to the limitations of the human response to deep breath-hold diving (Ferrigno et al., 1997).

According to a review by Ponganis, McDonald, Tift, and Williams (2017), factors that may influence the intensity of the DR include baroreceptor reflexes, pulmonary stretch receptor reflexes, trigeminal/glossopharyngeal nerve stimulation, carotid body receptor responses, blood gases, volitional control and exercise (Angell-James et al., 1978, 1981; Davis and Williams, 2012; de Burgh Daly et al., 1977; Elsner, 1965; Elsner et al., 1977, 1964; Grinnell et al., 1942; Jobsis et al., 2001; Ridgway et al., 1975; Signore & Jones, 1996 as cited by Ponganis et al., 2017). These mechanisms are particularly exaggerated in breath-hold divers and assist in increasing diving durations by temporarily reducing peripheral tissue oxygen uptake (Valic et al., 2006).

During apnea, there are two distinct phases which contribute to the physiological breaking point, at which rising concentration of CO₂ in the blood triggers “involuntary breathing movements” (Hentsch & Ulmer, 1984; Lin, 1982). The first is the “easy-going” phase and the second the “struggle phase”. During the easy-going phase, the diver experiences reduced levels of breathing urges whilst during the struggle phase, the diver experiences an urge to breathe followed by progressive involuntary breathing movements and a final “fighting” phase usually experienced by elite divers (Andersson & Schagatay, 2009; Dejours, 1995; Dujic & Breskovic, 2012; Steinberg, Pixa, & Doppelmayr, 2012). The “individual breaking point” marks the termination of apnea in which the need to breathe can no longer be resisted voluntarily (Dejours, 1965). The length of the easy-going phase is primarily
dependent on the accumulation of arterial PaCO₂ and less dependent on arterial PaO₂ (Andersson & Schagatay, 2009).

The DR has an oxygen conserving and dive prolonging effect (Schagatay & Anderson, 1998). Initiated by apnea, the response is transmitted via either a decrease in lung stretch receptor activity or direct contact between respiratory and cardiovascular control centres (Elsner & Gooden, 1983). Several researchers maintain that one’s breaking point can be postponed by changing the physiological conditions in the blood or by increasing one’s tolerance to such conditions. Irving (1963) who initially observed the diving response in humans, reported that the bradycardia of trained free divers was more pronounced compared to that of untrained subjects. Hong and Rahn (1967) in their study also reported pronounced bradycardia in the Ama divers when compared to other participants.

Whilst the DR is involuntary, Schagatay and Andersson (1998) suggest that the DR can be trained and can have positive effects on both HR reduction and apnoeic duration. Training effects have been observed in pearl, shell and sponge divers as well as athletes in the sport of free diving, which is the sport of diving on one breath. Long term training of free diving is associated with a number of physiological adaptations including a more exaggerated DR, and greater lung volume, lung O₂ and CO₂ stores (Schagatay & Anderson, 1998; Ferretti & Costa, 2003). The HR of human BH divers can decrease more than 50% whilst diving (Ferrigno et al. 1997). Undoubtedly the training undertaken by professional free divers has contributed to their exceptional breath-hold ability, as evidenced by the world record free diving depths humans have been able to achieve.
2.3 BREATH-HOLDING AND COLD FACIAL IMMERSION

Cold facial immersion (CFI) alone is sufficient in contributing to the oxygen-conserving effect of the DR (Anderson et al., 2016; Lemaitre et al., 2008). During CFI, receptors that are supplied by the trigeminal nerve transmit this information to the brain and subsequently innervate the vagus nerve that is part of the ANS (Nepal, Sharma, Mander & Kusma, 2015). The mechanisms underlying increases in blood pressure due to CFI is likely the result of sympathetic nervous system (SNS) activation. Increases in SNS activity elicits responses that include, vascular resistance in the peripheral (Fisher et al., 2015; Heistad, Abbound & Eckstein, 1968), visceral (Espersen et al., 2002; Patel, Mast, Sinoway & Muller, 2013) and cerebral (Brown, Sanya & Hilz, 2003) vasculatures, all of which contribute to increases in blood pressure (Fisher et al., 2015; Khurana & Wu, 2006; Patel et al., 2013; Shamsuzzaman et al., 2014; Stemper, Hilz, Rauhut & Neundorfer, 2002). An increase in SNS activity as a result of CFI is related to multiple mechanisms through which increases in stroke volume occurs (Datta & Tipton, 2006; Gagnon et al., 2013; Gooden, 1994; Jay et al., 2006; Paton et al., 2005; Schlader, Coleman, Sackett, Sarker & Johnson, 2016).

According to Nepal et al. (2015), exposing the peripheral skin to cold stimulus is also sufficient in eliciting a DR, further stating that stimulation of the trigeminal nerve around the facial region is not the only method in eliciting DR. A study by Andersson et al. (2000) concluded that while HR reduction and selective vasoconstriction brought about by BH without immersion were augmented by CFI, forearm immersion in water as apnea begins had no effect on eliciting the DR. The study also revealed that cold-water immersion augmented the reduction in skin capillary blood flow, suggesting that cold stimulation is an effective method in
provoking reflex vasoconstriction in the skin. Regardless of the site of stimulation, cold stimulation leads to vasoconstriction in the skin vessels that is not affected or augmented by concurrent cold stimulation to another part of the body (Andersson et al., 2000).

The peripheral chemoreceptors’ primary purpose in humans is in detecting and responding to an increase in partial pressure of carbon dioxide (PaCO₂) and decreases in pH or in PaO₂ (Alboni et al., 2011). During apnea, peripheral chemoreceptors are stimulated by the lack of consistent afferent stimuli directed from the pulmonary stretch receptors leading to hypoxia. The response of the cardiovascular system includes bradycardia, vasoconstriction, and secretion of suprarenal catecholamine. Conversely, during facial or whole body immersion, the accompanying bradycardic response is not attributed to the peripheral chemoreceptors, but instead is a manifestation of the DR. In this instance, the arterial PaO₂ and PaCO₂ are within normal range, hence the bradycardiac response is independent of chemoreceptor stimulation and is triggered exclusively via breath-holding and through cutaneous cold receptors. However, findings of previous research suggest that the chemoreceptor stimulation during prolonged hypoxic dives may play a part in accentuating bradycardia (Alboni et al., 2011).

Diving stimulates synergistic sympathetic and parasympathetic responses responsible for the heightened cardiovascular reflexes in humans, which when compared to cold facial stimulation and breath-holding alone, produce a greater response than the sum of individual responses (Andersson et al., 2000; Shamsuzzaman et al., 2014). The exact mechanisms by which the peripheral nervous
system is activated by apnea remains undetermined. Potential explanations include activation of baroreflex, activation of the lung inflation reflex and normalization of blood gases, as well as hypoxia and hypercapnia playing an important part in the stimulation of chemoreceptors (Foster & Sheel, 2005; Lemaitre, Buchheit, Joulia, Fontanari & Tourny-Chollet, 2008). It is thought that the interplay of various interacting factors such as baroreceptors, pulmonary stretch receptors, lung volume, blood gases, pulmonary shunting and associated hydrostatic pressures influence the bradycardiac effect of the DR (William et al., 2015).

Studies have demonstrated that decreases in heart rate are much greater with facial immersion while breath-holding (Nepal et al., 2015; Andersson & Schagatay, 1998). This can be explained by the stimulation of the trigeminal nerve around the facial and neck region. The cold sensation stimulates the afferent pathway of the trigeminal nerve causing stimulation of the cardiac centre located in the medulla resulting in bradycardia (Nepal et al., 2015). Apnea with face immersion producing intense bradycardia and marked vasoconstriction can lead to lowered O₂ consumption and decreased CO₂ (Andersson & Schagatay, 1998; Andersson et al., 2002). Due to increased bradycardia, the metabolic demand for the cardiac muscle is lowered and marked vasoconstriction leads to reduced O₂ consumption by tissues, which during apnea with cold facial immersion, results in a smaller degree of arterial haemoglobin desaturation as compared to apnea in air (Andersson & Schagatay, 1998).

In a study by Andersson and Schagatay (1998), the level of arterial haemoglobin desaturation observed was lower after apnea with face immersion, than after apnea alone suggesting that O₂ consumption was reduced due to a stronger DR
elicited during apnea with face immersion. A study measuring neural and circulatory responses during simulated diving in humans found that clear and significant bradycardia was not evident during either facial immersion or apnea alone, suggesting the importance of both these stimuli in eliciting “combined cardiac vagal outflow and central sympathetic outflow” (Shamsuzzaman et al., 2014, p.77).

Whilst the DR is activated by apnea, it is significantly augmented by face immersion in cold water in which cold-receptors in the upper facial region (forehead, eyes, and nose) are stimulated (Gooden, 1994; Schagatay & Anderson, 1998). These facial regions are supplied by the trigeminal nerve which when stimulated causes the inhibition of respiration and stimulation of cardiac vagal motor neurones and vasomotor centres (Elsner & Gooden, 1983). The cardiovascular responses further enhance the DR by reducing HR and vasoconstriction occurring during a dry BH (Anderson, Liner, Runow & Schagatay, 2002). In particular, research indicates facial cold receptors are more strongly innervated by immersion in water with a temperature ranging 10 – 15 °C (Daly, 1997). Colder water temperatures 0-10 °C have demonstrated to elicit a more pronounced bradycardiac effect, (Schagatay & Holm, 1996; Anderson et al., 2016), however lower temperatures are associated with more physical discomfort (Manley, 1990). Water temperatures between 15 and 35°C have been shown to have little effect (Asmussen & Kristiansson, 1968; Mukhtar & Patrick, 1986). More recently the difference between air ambient temperature and water temperature has also been found to be an important determinant in the activation of the DR. Diving bradycardia also develops in warm water however when the ambient air temperature is higher and there is a marked gradient between air and water (Schagatay, 2009).
The DR has also been used as a laboratory procedure in experimental designs and is also referred to as the simulated diving response. Given that the simulated DR produces pronounced reflex bradycardia it has been used to treat paroxysmal atrial tachycardia and has been utilised as a method to diagnose vagal dysfunction (Khurana & Wu, 2006). Inputs from several sources including the trigeminal nerve, chemoreceptors, arterial baroreceptors, cardiac and pulmonary receptors and higher centres of the brain co-operate to elicit bradycardia. Relatively little is known about the underlying mechanisms of the cold facial immersion task also known as the cold facial test. It is thought that the trigeminal system and the brain stem are implicated in the bradycardia response (Khurana & Wu, 2006).

It may be presumed that some of the neurobiological areas including the chemoreceptors and baroreceptors which have been found to play an active role in CO₂ sensitivity, hypercapnia, and alkalosis, and Klein’s suffocation false alarm (SFA) hypothesis in understanding the pathophysiology of panic may also be responsible for the bradycardiac response in the cold facial immersion task. No research to date has looked at whether the DR adaptation can be used to treat panic or any of the other anxiety disorders. Given that most PD patients have respiratory abnormalities it would be important to further explore the association between PD and hypersensitivity to increased CO₂ levels. The CO₂ challenge should be considered among the most valuable anxiogenic challenge test that can also be used as a diagnostic tool, to identify patients with PD (Gorman et al., 1994).

During hyperventilation, there is a significant decrease in blood flow, due to vascular constriction caused by hypocapnia. This accounts for many of the symptoms
experienced during hyperventilation including lightheadedness, dizziness, derealisation and anxiety (Gorman et al., 1994). In humans, the cerebral blood flow reduction is observed to be between 5% and 15% (Edvinsson, 1982). Panic patients have been noted to have more sympathetic stimulation in the periphery, which is implicated by the reduction in the cerebral blood flow (Nesse et al., 1984). Reduced cortical volume in the dorsal anterior cingulate cortex, as well as the rostral anterior cingulate cortex, has been observed in PD patients (Asami et al., 2008). The anterior cingulate cortex is responsible for regulating autonomic responses such as heart rate and blood pressure, and it is involved in problem solving (Asami et al., 2008). On the contrary, when the diving response (DR) is activated cerebral blood flow is increased dramatically, in an attempt to conserve oxygen and ensure that the organs most important for survival are oxygenated adequately, hence problem-solving ability may increase. Elite divers have exhibited higher blood circulation in the brain and a more accentuated DR (Joulija et al., 2009). Brain capillaries in divers are more dilated to allow for increased blood flow, as a result of trained effects and prolonged exposure to hypobaric conditions (Chavez et al., 2000).

Charles Darwin (1872) in his book the ‘Expression of Emotions in Man and Animals’, wrote that “heart, guts and brain communicate intimately via the vagus nerve the critical nerve involved in the expression and management of emotions in both humans and animals”. When the mind is strongly excited, it instantly affects the state of the viscera. Darwin described that expressions of emotions derived their communicative value from the fact that they were outward manifestations of inner state behaviour and that these served an advantageous purpose in natural selection (Tooby & Cosmides, 1990). William James was strongly influenced by Darwinian
ideas, and he proposed that emotions are simply sets of physiological changes that result in response to emotive stimuli and that it is the perceived bodily changes that evoke the feeling of an emotion (Friedman, 2010).

Approximately 80% of the fibres connecting the viscera to the vagus nerve are afferent, meaning that the body communicates via sending signals to the brain through this single direction (Martini et al., 2012). Stimulation of the vagus nerve has important implications in inhibiting sympathetic nervous system (SNS) activity and may enhance extinction in fear conditioning (O’Keane, Dinan, Scott & Corcoran, 2005; Porges, 2009). Noble et al. (2017) in their study found that stimulating the vagal nerve in post-traumatic stress disorder (PTSD) rats, reduced PTSD symptoms including re-experiencing fear, heightened anxiety, physiological arousal and social withdrawal. Their findings suggest that vagal nerve stimulation may be an effective adjunct to exposure therapy which may be used for PTSD and the anxiety disorders that benefit from exposure-based treatments. In anxiety disorders such as PTSD and PD which are characterised by more exaggerated fear and freezing responses, SNS arousal increases metabolic output and inhibits peripheral nervous system/vagal tone in an attempt to activate the fight or flight response. Alternative therapies that initiate movement such as yoga and floating therapy that are thought to stimulate the vagal nerve are becoming increasingly popular for disorders characterised by immobilisation such as PTSD, PD and major depressive disorder (Cramer, Anheyer, Saha & Dobos, 2018). Another alternative to stimulating the vagal nerve is using the DR as it involves vagal-mediated activity and balances sympathetic and parasympathetic nervous system responses in an attempt to conserve oxygen and increase survival chances for the organism.
2.4 FREE DIVING AND BREATH-HOLDING

Free diving, also known as breath-hold (BH) diving is the sport of diving on one breath. It has been practiced for more than 2000 years in Greece, India, Japan, Korea and Persia (Ferretti, 2001). Having evolved from the ancient traditions of harvesting sponges, pearls and seafood, today, free diving is considered an extreme sport in which competitors attempt to reach great depths on one breath without the assistance of underwater breathing equipment. Humans are not natural breath-holders, just like other birds and mammals and hence a lack of oxygen, even for short periods can be detrimental. However, many diving birds, mammals (e.g., Weddell seal) and humans have adapted to endure hypoxia or anoxia for extended periods (Hermes-Lima & Zenteno-Savin, 2002).

Free divers are known to have exceptional breathing control, with higher brain function being associated with a profound effect on the development of the DR (Gooden, 1994). According to Mana (2010), free diving is able to improve the neurovegetative system, specifically our breathing and respiratory rate, our heart and lung function. Anecdotally, some of the benefits free divers claim they achieve from regular free diving include mental clarity, relaxation, thoracic flexibility, and emotional wellbeing. Free divers draw on a range of techniques to assist them to attain greater depths underwater and both the dry training breathing techniques and the breath-hold practice in the water stimulate the parasympathetic system and restore the neurovegetative balance such as increased vagal tone (Christoforidi et al., 2012). In particular, some of the breathing and relaxation techniques used in free diving have been effective in activating the parasympathetic nervous system and slowing down the heart rate (HR). More specifically, due to the exchanges of gases achieved by
better breathing control, it promotes more efficacious cellular oxygenation which extends to better functioning of the nervous system with general and deep body revitalisation (Mana, 2010).

Extensive training of BH diving or apnea is associated with several physiological adaptations including longer breath-holding dives, a more pronounced diving response (DR), larger vital capacities and blunted hypocapnic response than control participants which were non-divers (Andersson & Schagatay, 2009; Carey, Schaefer & Alvis, 1956; Ferretti & Costa, 2003; Schagatay & Anderson, 1998). In a more recent study, Schagatay, Johansson and Abrahamsson (2017) investigated trained effects in 9 male Philippine Sama-Bajau divers and found that the DR was more pronounced in divers as compared to non-divers. Although lung vital capacity was comparable to non-divers, lung function effects were observed in divers.

Regular free diving practice brings physiological dynamism and builds resistance to existing stress factors (Mana, 2010). Foster and Sheel (2005), stated that healthy individuals that engage voluntarily in BH activities, display adaptations that enable longer BH durations and a more pronounced DR. Ferretti (2001) in his study found that trained BH divers will endure a breath-hold until PaO₂ has fallen to 35 mmHg and PaCO₂ has increased to 50 mmHg which is more adapted than in non BH divers. There are also varying levels of CO₂ tolerance and individual sensitivity to CO₂. Vagin and Zelenkova (2017) in their study, explored the physiological mechanisms of hypoxia tolerance and physical endurance in free divers, basketball players and untrained participants. The findings revealed that free divers possessed the greatest tolerance to hypoxia and showed the highest physical work capacity
compared to other groups in this study. Free divers were also observed to have had the highest fall in oxygen saturation (SaO₂) values and were the only group to perform between three to eight breath-holds while still active on the cycle ergometer (Vagin & Zelenkova, 2017). In their experiment, Baranova et al. (2016) discovered that inhalation of 7% hypercapnic mixture led to variations in measures and magnitude of changes of cerebral blood flow (CBF) indicating varying levels of sensitivities to stimulus amongst participants.

### 2.4.1 Individual Determinants in Breath-Hold Diving

One area of contention is in establishing whether elite performance in BHD, tolerance to CO₂ and diminished respiratory drive under hypercapnia may be hereditary or the result of an adaptation due to frequent short-term exposure to hypercapnia (Walterspacher, Scholz, Tetzlaff & Sorichter, 2011). The world records and boundaries of breath-holding and diving depths have been challenged and “pushed further” in the last decade, exposing breath-hold divers to frequently severe hypercapnia and hypoxic conditions (Walterspacher et al., 2011).

Ferringno et al. (1991) investigated the physiological responses to dives down to 65 meters in 3 elite BH divers, all of whom were from the same family. Results revealed that all three divers demonstrated marked bradycardia (20-25 beats per min) compared to untrained controls. However, according to Ferrigno et al. (1997), physiological observations obtained from the DR may not necessarily be the result of physiological adaptation, but rather the expression of genetic factors (Ferrigno et al., 1997). According to Alboni et al. (2011) studies have revealed that compared to inexperienced divers, BH divers demonstrate more pronounced bradycardia. These
notable differences between groups may be accounted for by the training and the genetic differences between them.

In exploring the mechanisms of the DR, recent genetic studies suggest that the intensity of vasoconstriction experienced during the activation of the DR is subject to interpersonal differences. Baronova et al. (2017) in their study investigated the genetic components of the vascular reactions in response to the DR and conducted a genetic analysis of the polymorphisms of renin-angiotensin, kinin-bradykinin genes and the gene β2-adrenoreceptor (ADRB2). They found that during the DR, changes in blood pressure (BP) and vascular tone in participants were dependent on their genotype. More specifically, this study found that participants with the most pronounced peripheral vasoconstriction in response to diving had BDKRB2 (C/C), ACE (D/D) and ADBR2 (G/G, G/A) genotypes. This study concluded that changes experienced by participants in the vascular tone and BP were dependent on their genotype (i.e., different combinations of alleles of the studied genes) (Baranova et al., 2017).

Individual differences such as age and diving experience influence the extent of DR. The diving bradycardia is pronounced in children between ages 4 and 12 months, as this may assist children in surviving through “hypoxic episodes proximal to birth” (Lindholm & Lundgren, 2009, p. 285). With advancing age, the DR weakens and is more pronounced in experienced and habitual BH divers than non-divers (Lindholm & Lundgren, 2009; West et al., 2001). A study by West et al. (2001) found that 11-14-year olds exhibited a greater reduction of HR after cold facial immersion (CFI) as compared to adults, further stating that with advancing age, the
extent of HR reduction weakens. This has also been confirmed in a study by Lee et al. (2016) of elderly Korean women divers, or haenyeos, aged between 56 and 83 that demonstrated lower mean HR with about 20% decrease rate in HR during dives as compared to younger haenyeos in a previous study (Hong, Song, Kim & Suh, 1967) that demonstrated reduction of 21% and 37% decrease in HR.

Psychological and physiological factors play a role in increased breath-holding time (Andersson & Schagatay, 2009). Prolonged breath-holding not only elicits extensive physiological changes, but also requires exceptional psychological states and therefore breath-holding is thought to be a unique psycho-physiological state (Steinberg, Pixa, & Doppelmayr, 2012; Schagatay, 2009). Besides physiological capabilities, psychological factors are important aspects of BH diving, as mentally, free divers need resilience to pain, physical exertion, withstanding extreme environmental conditions, and coping with dangers to health and possible loss of life (Ostrowski et al., 2012; Schagatay et al., 1999; Schagatay, van Kampen, Emanuelsson, & Holm, 2000). Rodriguez-Zamora et al. (2014) suggest that an interrelationship exists between psychological factors and physiological stress experienced by synchronised swimmers during competitive events.

In trained apnea divers, duration of the easy-going phase is extended due to training induced adaptations, while humans not trained in BH usually end apnea at the start of the struggle phase (Steinberg et al., 2012). In the easy-phase of breath-holding, physiological factors such as tolerance to increasing PaCO₂, determines duration of BH, while significant mental effort is necessary to maintain BH through the discomfort of asphyxia in the struggle phase requiring motivation, stamina,
emotion regulation and cognitive factors that includes inhibition and interoception (Steinberg et al., 2012). Mental predispositions and psychological capacity to tolerate the discomfort and urge to breathe strongly influences breath-holding durations in the struggle phase (Ostrowski et al., 2012; Schagatay et al., 1999; Schagatay et al., 2012).

There is scant research on the characteristics of free divers; however, research examining the characteristics of recreational scuba divers can provide some indication into understanding free divers. Research indicates that the proportion of female and males engaging in scuba diving activities is 29% and 71%, respectively (Morgan, 1987; Morgan, Lanphier, & Raglin, 1989). In the Morgan Study (1987), the average age of both subgroups was 34 years, with the men averaging 7 years of diving experience compared with 5 years average diving experience in women. Both subgroups performed dives in a range of settings including fresh water, salt water, cave, ice and shipwreck diving, with the average maximum depth being 34 m for females and 36 m for males. Further examination of trait anxiety and mood states indicated there were no significant differences in both trait anxiety and mood states between males and females (Morgan, 1987; Morgan et al., 1989). There is a general belief that recreational activities such as free diving and scuba diving can be stressful and hence that these types of activities are characterised by high anxiety. However, this assertion is not supported in the literature. On the contrary, it has been found that students enrolled in beginner scuba classes have been found to report below the norm on state and trait anxiety as measured by the State and Trait Anxiety Inventory (STAI) (Griffiths, Steel, & Vaccaro, 1978).
From an anxiety sensitivity (AS) perspective, panic disorder (PD) is associated with an enduring trait-like characteristic in individuals which leads to cognitive misappraisal of somatic symptoms as threatening (McNally, 1994; Reiss, 1991). According to this theory and in line with the findings of Griffiths et al. (1978), it would be expected that AS and trait anxiety would constitute characteristics that differentiate free divers from individuals with PD. Free divers would be expected to report low AS and trait anxiety as compared to high AS and high trait anxiety in individuals with PD.

2.5 ADAPTIVE CHANGES DURING BREATH-HOLD AND APNEA TRAINING

There have been numerous studies conducted on breath-holding over the years, many of which have focused on the physiological aspects of breath-holding. Yet despite constant improvements in the performance of elite free divers that are capable of diving beyond depths imaginable, many questions regarding these demonstrated performance increases are still unanswered (Steinberg, Pixa & Dopplemayr, 2012). Indeed elite breath-hold divers are capable of such extraordinary feats, however, the question is whether the abilities they possess are inherited or developed through training? This section focuses on exploring the effects of short-term and long-term breath-hold (BH) training and the adaptive changes associated with it.

Improvements in performance and age differences between previous and current world record holders point to the adaptive capabilities of humans, progress in devices, training techniques, and technical progress (Ostrowski et al., 2012). There
have been multiple studies (Adir et al., 2004, 2005; Andersson & Schagatay, 2009; Breskovic et al., 2010; Delahoche et al., 2005; Engan et al., 2011; Gole et al., 2009; Lemaitre et al., 2009; Lemaitre et al., 2010; Mourot et al., 2009; Schagatay et al., 1999; Schagatay et al., 2000; Steinback et al., 2010; Vigetun – Haughey et al., 2015) investigating the short-term and long-term training effects of the DR, with many attributing short-term training effects to psychological and physiological factors. A review by Konstantinidou and Chairopoulou (2017), reported several long-term physiological adaptations resulting from apnea training effects. Figure 3 depicts how long term apnea training may alter the diving response (DR).

Figure 3. Long-term training effects of the Diving Response (Konstandinou and Chairopoulou, 2017).

Individuals that engaged in regular breath-hold training (BHT) had a stronger DR, larger lungs and vital capacities, stronger respiratory muscles, haematological variations such as an elevated haematocrit and haemoglobin, and reduced blood
acidosis. Moreover, the apnea-trained individuals were observed to have reduced chemosensitivity to hypoxia and hypocapnia, reduced respiratory drive and increased blood circulation to the brain. Konstantinidou and Chairopoulou (2017), suggest that most researchers, attribute the variations in physiological responses observed in apnea trained individuals as compared to non-apnea trained individuals, to hypoxic conditioning and the DR. Figure 4 depicts the characteristics and responses exhibited by apnea trained individuals that may account for the increased tolerance to hypoxia and potentially for their increased aerobic and anaerobic performance.

![Diagram of APNEA TRAINING AND CHRONIC RESPONSES]

*Figure 4. Long-term physiological adaptations in apnea-conditioned individuals (Konstandinou and Chairopoulou, 2017).*

Nevertheless, the mechanisms behind these adaptations have not yet been completely clarified, and hence it is recommended that future research should clarify
the physiological mechanisms involved that lead to altered responses to hypoxia between apnea-trained and non-apnea trained individuals (Konstandinou & Chairopoulou, 2017).

According to Tipton (2016), the most common questions regarding adaptation includes, “how long does it take”, and more importantly, “how long does it last?” (p. 10). Two techniques are commonly used in inducing adaptations; the first being repeated achievement of a constant physiological strain (e.g., deep body temperature, heart level, level of exertion) or repeated exposure to a constant stimuli, while the second aims to maintain the stimulus to adapt and delivers more effective physiological adaptation (Taylor, 2014). Whilst the DR is involuntary, Schagatay and Andersson (1998) suggest that the DR can be trained and it can have positive effects on both heart rate reduction and apnoeic duration.

It has been well established in the literature that BH divers have more of a pronounced DR. Coastalat et al. (2016) attributed this to simultaneous shifts in both cardiac and peripheral hemodynamics taking place at the halfway point of the breathhold as measured by kinetics analysis. Structural changes have also been identified in the heart, as evidenced by an increase in the size of heart chambers, resultant from training effects and cardiovascular adaptive changes (Zelenkova & Chomahidze, 2016). In a study investigating cardiac autonomic activity in free diving (FD) athletes, Christoforidi et al. (2012) revealed that when compared to an untrained control group, free divers exhibited higher sympathetic and enhanced cardiac parasympathetic tone four days after the last BH dive. This was the first study to show that as a result of exercise training and repeated exposure to FD stimulus, the
vagal tone and resting cardiac autonomic activity is significantly higher in FD athletes. There is however a gap in the literature exploring long-term cardiac autonomic adaptations in free divers.

Physical and apnea training are both vital components of active diving performance. A study by Schagatay et al. (2000) demonstrated that of these two modes of training, frequent exposure and performance of apnea is better at assisting in increasing BH time by delaying the physiological breaking point and enhancing bradycardia. Schagatay et al. (2000) demonstrated that two weeks of daily apnoeic training increased both the DR and the duration of BH. In non-divers, even short term repetitive breath-hold training (BHT) has demonstrated a positive effect on BH duration without changing the magnitude of the DR, nor its oxygen-conserving effect (Schagatay, van Kampen & Andersson, 1999). Adaptations of the cardiovascular system to physical training results in increased O₂ delivery to the muscles enabling intense aerobic physical exercise, while adaptive changes are also exhibited at the muscular level allowing increased extraction of O₂ (Schagatay et al., 2000).

Short-term and long-term apnea training and physical training have demonstrated adaptations to diving conditions and augmentation of arterial compliance function. There are two major functions of the arterial system; the first is the delivery of nutrients and oxygenated blood to organs and the second function is to act as a buffer in softening pulsations from the heart to allow continuous capillary blood flow (Steppan, Barodka, Berkowitz & Nyhan, 2011). Arterial compliance can be defined as the relationship between changes in vessel dimension for a given change in pressure or distending pressure (Anderson, 2006; Kinlay et al., 2001). There are
several factors that can alter arterial circulation after a dive such as cold water immersion and hyperoxic exposure, (Gole, Louge & Boussuges, 2007).

Biological aging and atherosclerosis are two contributing factors towards arterial stiffness that are typically found in pathological conditions that include diabetes, chronic kidney disease, isolated systolic hypertension and atherosclerosis (London & Pannier, 2010). Tanaka et al. (2016) investigated the effects of chronic diving manoeuvres on arterial elasticity, structure and function of Japanese female pearl divers (Ama divers). The Ama divers were found to possess significantly lower arterial stiffness and values in indices of arterial wave reflection, and higher subendocardial perfusion as compared to non-Ama, which point to lower cardiac activity. Based on the results of this study, it seems that regular diving manoeuvres are associated with favourable adaptations in arterial elasticity, wave reflection, and reduced risks of cardiovascular based diseases (Tanaka et al., 2016).

Vascular modifications induced as a result of physical training are dependent on the training modalities (Gole et al., 2007). Increases in central arterial compliance have been observed as a result of regular endurance exercise, which is attributed to changes in vascular endothelium-derived factors (Cameron & Dart, 1994; Tanaka, Dineno & Monahan, 2000; Hayashi, Sugawara & Komine, 2005). According to Gole et al. (2007), previous studies have shown that acute endothelial alteration can be induced after a single dive. The endothelium plays a crucial role in maintaining vascular homeostasis by achieving a balance between endothelium-derived contracting and relaxing factors, and also through the release of paracrine factors that act on platelets, inflammatory cells and the vessel walls (Anderson, 2006).
Previous research has demonstrated a decrease in plasma concentrations of endothelin-1 (vasoconstrictor peptide) produced by vascular endothelial cells in endurance-trained men (Otsuki, Maeda & Lemitsu, 2007; Maeda, Miyauchi & Kakiyama, 2001). Vascular endothelial function is important for the growth and maintenance of the health of blood vessels, and for the regulation of immune responses (Gole, Lounge & Boussuges, 2007). Endurance training has also been associated with an increase in concentrations of nitric oxide, an important cellular molecule that modulates vascular tone and reactivity (Anderson, 2006; Assumpção et al., 2008). Nitric oxide is the product of synthesis from L-arginine and the enzyme nitric oxide synthase (NOS) which has multiple functions such as insulin secretion and vascular endothelial function by keeping the vessels flexible and dilated in order to boost blood flow and regulate blood pressure. Furthermore, its functions extend to protecting the arterial walls of blood vessels and inhibiting white cell and platelet activation from adhering to the lining of the blood vessels, hence reducing the risk of plaque development (Anderson, 2006; Assumpção et al., 2008; Kingwell, Sherrard & Jennings, 1997; Maeda, Miyauchi & Kakiyama, 2001).

One of the benefits of training effects associated with repeated apneas is prolonged breath-holding time as a result of blunted hypercapnic response (Andersson & Schagatay, 2009; Roecker et al., 2014; Walterspacher et al., 2011). Grassi et al. (1994), observed that divers exhibited a diminished ventilatory response to hypercapnia. The hypercapnic ventilatory response curve measures CO₂ sensitivity (Andersson & Schagatay, 2009). In a variety of athletes, including elite endurance and BH athletes, reduced chemosensitivity to progressive hypoxia and hypercapnia
has been noted (Foster & Sheel, 2005). According to Andersson and Schagatay (2009) reduced sensitivity to CO₂ observed in divers is not a trait that is genetically inherited; instead, it is caused by training of BH diving. Studies investigating instructors working at a submarine escape training tank have provided evidence to support this (Schaefer, 1965).

Ferretti and Costa (2003) postulated that the prolonged breath-holding time demonstrated by trained divers may be due to a displaced threshold and reduced sensitivity to CO₂ as a result of frequent exposures to hypercapnia leading to a reduced urge to breathe. Trained breath-hold (BH) divers will endure the human diving response during a BH until PaO₂ has fallen to 35 mmHg and PaCO₂ has increased to 50 mmHg whereas non-divers when engaging in BH activity, can generally reduce their arterial partial pressure of oxygen (PaO₂) as low as 60 mmHg and their partial pressure of carbon dioxide (PaCO₂) as high as 45 mmHg (Ferretti et al., 2001). Tolerance to CO₂ has also been demonstrated by trained synchronized swimmers who can sustain a normoxic BH for approximately twice the BH time as compared to non-diving controls (Bjurstrom & Schoene, 1987).

Studies have shown that only long-term exposures to hypercapnia results in blunted hypercapnic ventilatory response as evidenced by trained breath-hold divers (Costalat et al., 2014; Delapille et al., 2001; Grassi et al., 1994; Ivancev et al., 2007), Ama divers (Masuda et al., 1982), and underwater hockey players (Davis et al., 1987), while short-term training has no effect (Andersson & Schagatay, 2009). A study by Schagatay and Andersson (2009) investigating whether short-term training reduces the hypercapnic ventilatory response found that reduced CO₂ sensitivity was not a
contributing factor to the observed short-term apnea training effects. It has thus been predicted that repeated and prolonged bouts of intermittent hypoxia/hypercapnia may reset the chemosensitivities for both central and peripheral chemoreceptors, and enhance chemoresponsiveness to hypoxia (Costalat et al., 2014). The time course for the development of this adaptation to BH, that includes how many and how frequent these exposures are needed has not yet been investigated (Andersson & Schagatay, 2009).

In a study by Andersson and Schagatay (2009), prolonged breath-holding time observed as a result of short-term apnea training was attributed to changes in hematocrit and hemoglobin concentrations, suggesting that changes in hematocrit and hemoglobin concentration levels caused by splenic contractions could contribute to the short-term training effects observed further stating that the changes in hematocrit and hemoglobin concentration levels lead to a delay of the physiological breaking point of apnea (Andersson & Schagatay, 2009; Schagatay et al, 2001; Bakovic et al., 2003).

A study by Nygren-Bonnier et al. (2007a) investigated whether 6 weeks training in glossopharyngeal pistoning, (a technique used in free diving with an aim to piston more air into the lungs than able with maximum inspiratory capacity) would increase vital capacity in healthy women. The researchers found that vital capacity increased in the training group by 0.13 litres and the increase in vital capacity persisted for twelve weeks post-training. The mean vital capacity increase in the training group was by 3% after the six week training period (Nygren-Bonnier et al., 2007a). Divers that have undergone long-term specialized training in BH have also
demonstrated increases in the respiratory system’s functional parameters, which during prolonged BH diving, assist in delaying respiratory muscle fatigue (Nygren-Bonnier et al., 2007b). Bavis et al. (2007) draw on hypoxia research to suggest that the human respiratory of BH divers has plasticity on several levels, including increased lung capacity, diaphragmatic changes and biochemical shifts.

Joulia et al. (2009) postulated that apnea training provides hypoxic preconditioning and hence it may be potentially used to optimise hypoxia protection in various conditions such as hypobaric hypoxia exposure, chronic obstructive pulmonary lung disease (COPD), and asthma. One may speculate, that this may be further extended to respiratory abnormalities that involve a higher sensitivity to CO₂, including PD and sleep apnea. The exact underlying mechanism explaining increases in vital capacity is undetermined. However, this phenomenon may be the result of an increase in pulmonary compliance as a result of stretching experienced, thereby allowing inspiratory muscles to inhale to a larger lung volume (Kang, 2000).

Longitudinal changes observed in divers by Carey et al. (1956) led to the suggestion that training may be responsible for increases in lung volumes (as cited in Schagatay et al., 2012). Frequent exposure to swimming or high altitudes may account for an increase in lung volume capacities; however, this effect has not been demonstrated in other sports (Gaultier & Crapo, 1997). Specific training protocols and complex training programs developed by elite divers have also demonstrated benefits in increasing lung volume (Schagatay et al., 2012). Long-term exercise alone is not sufficient to enhance lung and respiratory capacities and requires underwater exercise training where the lungs are exposed to greater water pressure (Lee et al.,
A study by Bachman and Hovarth (1968) demonstrated that participants that undertook training as part of a four month swimming program demonstrated increased lung and respiratory capacities compared to participants trained in a four month wrestling program. According to Schagatay et al. (2000) similar to the concept of specificity, training effects that are expressed are training-specific and dependent on the type of training that was performed.

Breath-hold training (BHT) has also shown to induce adaptive metabolic responses to repetitive periods of hypoxaemia. A longitudinal study by Joulia et al. (2003) investigating the benefits of a 3-month training program of dynamic apnea found that as a result of training, static apnea lengthened in duration along with accentuated bradycardia. A decrease was also found in venous blood pH and an increase in lactic acid concentration post-apnea. The study also showed the training suppressed oxidative stress following both static and dynamic apnea, increased tolerance to hypoxemia independent of any genetic factor. According to Joulia et al. (2003), exposure to intermittent asphyxia even in the short-term causes a sympathetic activation that continues after the removal of the chemical stimuli, serving as an explanation as to why the DR was accentuated after BHT. Results from this study suggest that exposure to intermittent asphyxia during BHT enhances the mechanisms protecting against membrane lipid peroxidation and reduced oxidative stress. The adaptive mechanisms responsible for the protection of tissues against the harmful effects of reactive oxygen species at rest requires prolonged exposures to hypoxemia. The findings of Joulia et al. (2002), suggest that the tolerance to extended apnea duration can be explained by post-training effects resulting in the reduction of lethal cellular consequences of blood acidosis and oxygen free radicals production.
Plasticity in the neural control of breathing is an important biological strategy used to preserve optimal breathing control (Fuller, 2017). One can learn quickly to voluntarily use their diaphragm and can readily achieve a habitual pattern of diaphragmatic breathing (Demoule et al., 2008). Metaplasticity changes have occurred as a result of training dependent plasticity on many levels including corticospinal changes (Raux, 2007). New discoveries which have included the impact of intermittent hypoxia on non-respiratory alpha motor neurons involved limb and other motor functions (Dale et al., 2014) derived from the study of respiratory motor plasticity has inspired new therapeutic strategies to treat motor deficits in multiple clinical disorders that compromise movement.

Trained effects have also been evidenced in physiological changes in winter swimmers. Whole body immersion in cold water also activates the DR and is associated with reduced oxidative stress (Lubkowska et al., 2013; Mila-Kierzenkowska et al., 2009), decreased levels of lipid peroxidation (Wozniak et al., 2013), and increased stimulation of antioxidant capacity (Lubkowska et al., 2013; Sutkowy, Wozniak, Boraczynski, Mila-Kierzenkowska, Boraczynski, 2015). Cold water exposure has been considered for centuries a traditional form of body hardening, which is considered to build up resistance to infections and illness (Siems, Brenke, Sommerburg & Grune, 1999).
2.5.1 Clinical Implications of the Diving Response

While changes in physiology produced by activation of the DR has been extensively explored and investigated, its clinical applications and implications need to be further explored. Clinically, the breath-hold (BH) task has frequently been used as a measure of distress (in) tolerance and self-regulatory strength (Steinberg, Pixa & Doppelmayr, 2012; Sutterlin et al., 2013). BH duration in this task is correlated with performance on neurobehavioural tests that quantify an individual’s ability in maintaining emotional and behavioural control (Sutterlin et al., 2013). It is possible that higher cognitive-control networks are involved in inhibiting the respiratory urge to breathe during BH that includes maintaining stable emotional states, sustaining motivation to reach BH goal while integrating unpleasant urges to breathe (Steinberg et al., 2012).

Breathing irregularity is a common symptom in patients suffering from panic disorder (PD) and other anxiety disorders. For some time now, it has been known that PD symptoms such as numbness, tingling sensations, dizziness, muscle hypertonicity could be brought on by hyperventilation and that these symptoms could be attributed to hypocapnia and respiratory alkalosis (Courtney, 2009). Breathing techniques are becoming increasingly popular and it has been found to be effective in regulating mental and emotional states. In many ways, the physiological adaptations experienced whilst free diving are the opposite of those triggered during a panic attack. Breathing techniques used in free diving have been effective in activating the parasympathetic system and slowing down the HR. Elevated HR is a common symptom in anxiety and panic states and it has been established that effective reductions in HR can provide substantial acute symptomatic relief for persons in such
states (Meuret et al., 2003). Given that the key factors in both free diving and panic attacks (PAs) are mental and breathing control, it is plausible that the diaphragmatic breathing techniques already used to treat panic may benefit from drawing on the physiological adaptions and techniques used in the sport of free diving.

A study by Yadav, Sule and Palekar (2017), which compared the effectiveness of airflow and facial cooling stimulation versus controlled breathing exercise (i.e., diaphragmatic exercises) to reduce dyspnea in patients with COPD, reported that facial cooling and airflow stimulation were more effective in relieving dyspnea. Shortness of breathing or dyspnea is characterized by impaired breathing that requires increased effort for breathing against increased resistance and in 85% of cases is the result of asthma, pneumonia, COPD, congestive heart failure, or psychogenic causes (i.e., PD, anxiety) (Yadav et al., 2017). Evidence suggests that the cold receptors located in the upper airway may be responsible for the reduced breathlessness as a result of facial cooling (Yadav et al., 2017). By detecting changes in temperature, cold receptors that are innervated with vagus nerve are able to monitor changes of flow in the upper airway (Yadav et al., 2017).

The DR has also been used in the treatment of paroxysmal supraventricular tachycardia (PVST). While the clinical application of the DR in managing PVST has gained acceptance in the medical community, evidence in the literature regarding its effectiveness is limited and results between studies vary greatly (Lemaitre & Schaller, 2015; Smith, Morgans, McD Taylor & Cameron, 2012). However, in the Smith et al. (2012) review, ten studies demonstrated that the human diving reflex is an effective technique used to treat PVST. The reflex bradycardic response elicited by the DR and
accompanying an increase in myocardial refractoriness “can be harnessed in a simple and non-invasive manoeuvre for the termination of paroxysmal supraventricular tachycardia (PVST)” (Smith et al., 2012, p. 611). The DR has also been utilized as a therapeutic procedure for children, in order to interrupt PVST after catheter ablation introduction, through facial immersion and is effective in 60-80% of cases (Mathew, 1981, as cited in Alboni et al., 2011). It can be difficult to distinguish between PVST and PAs as both are characterised by similar clinical symptoms, specifically both PVST and PAs present with rapid heart rate (Frommeyer, Eckardt & Breithardt, 2013).

2.5.2 Summary

The DR is an oxygen conserving adaptation allowing humans to hold their breath that far beyond normal times. Training with breath-holding and the DR have led elite free divers to achieve greater CO₂ tolerance when breath–holding. Much has yet to be determined about both the DR, its complex mechanisms involved, and the short term and long term benefits of BHT. Future studies are needed to determine whether the present physiological observations of the DR and adaptive training effects can be useful as a behavioural therapeutic approach in treating or managing psychological and physiological clinical conditions such as PD, COPD, asthma and sleep apnea, which are frequently associated with respiratory irregularities. Further investigation is needed in exploring the benefits of BHT and the treatment of PD.
Chapter 3

Respiration and Panic Disorder

3.1 RESPIRATION

Respiration is vital for the survival of the human organism, with every organ system relying on proper gas exchange (Wilhelm, et al., 2001). Respiration is an important consideration when studying PD as air hunger, dyspnea, and rapid breathing are common during PAs (Papp, Klein, & Gorman, 1993). Furthermore, irregularities and abnormalities in breathing are well documented in studies of PD and are important in understanding the pathophysiology of PD (Gorman et al., 1984; Griez, Lousberg, Van den Hout & Van der Molen, 1987; Woods et al., 1986).

The respiratory system provides humans with the fundamental ability to breathe, that is, to inhale and exhale air from the lungs. Breathing, also referred to as respiration, is fundamental to our survival. Whilst we possess to some extent the ability to consciously control the rate of breathing, it is a function that is instinctive and occurs automatically, without us having to think about it (Rogers, 2010). However, as simple as it is for us to inhale and exhale, respiration is a process supported by a number of complex functions including muscular movements, and cellular and chemical processes. Like any function of the body, breathing patterns may become dysfunctional or disturbed because of stress or illness (Rogers, 2010).
The term respiration includes two integrated processes including external respiration and internal respiration. External respiration refers to all the processes involved in the exchange of O₂ and CO₂ between the body’s interstitial fluids and the external environment (Martini et al., 2012). The main purpose of external respiration is to meet the respiratory demands of cells. Internal respiration is the absorption of O₂ and the release of CO₂ by those cells (Martini et al., 2012). Generally, the primary function of the respiratory system and normal breathing is to provide O₂ for the production of energy, maintain balanced blood pH levels, and a balance of CO₂ / O₂, for normal body functioning. An individual’s respiratory rate is defined as the number of breaths they take each minute. The normal respiratory rate of a healthy adult at rest ranges from 12 to 18 breaths each minute, which is roughly one breath for every four heartbeats. Children breathe at a more rapid rate, approximately 18 – 20 breaths per minute (Martini et al., 2012).

The respiratory system also works closely with the brain and the central nervous system. Both the diaphragm and chest muscles are stimulated by neurons that connect to the brain regions, the pons and medulla oblongata. Both these regions are intimately involved in the control of autonomic nervous activity and hence involved in the regulation of internal organs in the absence of conscious recognition or effort (Rogers, 2010). The most important input into the respiratory pattern generator comes from chemoreceptors that sense O₂ and CO₂. Under normal conditions, ventilation is primarily regulated by CO₂ levels rather than O₂. It is when oxygen becomes sufficiently low, in the case of lung disease or high altitude, that breathing is strongly stimulated and respiration increased. The peripheral chemoreceptors in the aortic and carotid bodies respond principally to a decrease in
blood oxygen. During hypoxia, the chemoreceptors also respond to the increased acidity that results from an increase in CO₂ (water and carbon dioxide combine to form bicarbonate and hydrogen ions). Afferent fibres from peripheral chemoreceptors travel in the glossopharyngeal and vagus nerves and communicate with neurons in the DRG (Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2013).

Central chemoreceptors in the brain stem respond to the decrease in the pH induced by an increase in CO₂ (hypercapnia) but do not respond to hypoxia. Serotonergic neurons are central chemoreceptors that are activated and located here due to their sensitivity to acidosis, and ability to sense hypercapnia in the blood. The reflex control of breathing can be modified behaviourally by the cortex, which receives information on respiratory movements and is able to alter ventilation by sending signals to the bulbopontine respiratory neurons and to spinal motor neurons (Feldman, 2011).

Respiratory sensations are affected both by respiratory movements and by changes in chemoreceptor activity. Sensations increase with ventilation, particularly with greater respiratory efforts per breath and also grow as the arterial PaCO₂ rises. This behavioural control which might act to modify ventilation and breathing patterns to minimise respiratory sensations could help achieve an optimum compromise between ventilation and PaCO₂ (Cherniack, Lavietes, Tiersky & Natelson, 2001).
3.1.1 Breathing and Chemosensitivity

The respiratory system’s basic functions are to transport $O_2$ to the organs of the body and to remove $CO_2$ which is the waste product in cellular metabolism. Although considered a waste product it plays a crucial role in maintaining acid-base homeostasis within the internal milieu of the body (Wilhelm et al., 2001). Lung ventilation which is determined by the rate and depth of breathing in humans is largely dependent on the partial pressure of $CO_2$ at normal levels of the partial pressure of oxygen ($PaO_2$) (>100 mmHg). When $PaO_2$ drops to very low values (<50mmHg) breathing is stimulated directly and is in turn more sensitive to an increase in $PaCO_2$ (Kandel et al., 2013).

To maintain homeostasis, physiological systems are subject to a number of chemosensory feedback mechanisms. While $O_2$ detection is taken care of by the peripheral chemoreceptors, $CO_2$ pH-sensitive chemoreceptors are found in the carotid bodies, and central chemoreceptors (CCRS) in the brain (Lopez & Garcia, 2007). Respiratory chemosensitivity enables the brain to detect changes in $CO_2$ and alter physiological systems to regulate its levels within tightly controlled parameters (Huckstepp & Dale, 2011). Most of the sensitive $CO_2$ cells are located in the brain, whilst a smaller amount is found in the carotid bodies (Peers & Buckler, 1995). The carotid body chemoreceptor cells are the sensory receptors responsible for hypoxia, hypercapnia and acidosis detection (Gonzalez, Almaraz, Obeso & Riguat, 1994; Peers & Buckler, 1995). $CO_2$/pH signals are related to the blood and its acid-base status and reflect the adequacy of breathing to metabolism (Lopez & Garcia, 2007).
PaCO₂ remains constant during physical exercise, and from well below to above sea level until prolonged periods of time are spent there or extreme altitudes are reached (e.g., a height greater than 762 metres). However, an increase in PaCO₂ by just 1 mm Hg causes a 20-30% increase in ventilation (Feldman, Mitchell, & Nattie, 2003) and increasing inspired CO₂ to 4% increases ventilation by 177% (Haldane & Priestley, 1905).

There are numerous physiological reflexes to protect against hypercapnia, which can be a life-threatening condition that leads to dangerous changes in pH levels and increased potential risk of asphyxiation. Better alveolar gas exchange may counteract the effects of CO₂ and improve with vasodilation and autoregulated organs (i.e., the brain and kidney). Renal output alters when blood CO₂ is high, which in turn conserves bicarbonate ions which act as a buffer for pH changes caused by hypercapnia (Huckstepp & Dale, 2011). Arousal from sleep and increased vigilance are common responses to elevated CO₂ (Buchanana & Richerson, 2010; Haxhiu, Toentino-Silva, Pete, Kc & Mack, 2001; Johnson et al., 2005; Williams et al., 2007) that either ventilation is insufficient or that there is a dangerous build-up of CO₂ that has resulted. According to Papp, Klein and Gorman (1993), the association of fear/anxiety to hypercapnia causes us to avoid or exit room areas where CO₂ levels exceed survivable limits.

Central chemoreceptors are found in the ventrolateral medulla, the nucleus of the solitary tract; the ventral respiratory group, the locus coeruleus (LC), the caudal medullary raphé; and the fastigial nucleus of the cerebellum (Nattie, 1999). Central chemoreceptors in the medulla control ventilatory motor output to maintain normal
blood CO₂. Serotonergic neurons within the raphe nuclei of the medulla may play this role by increasing the firing rate of the motor neurons when pH decreases because of an increase in PaCO₂. Serotonergic neurons are closely associated with large arteries in the ventral medulla so they are able to detect local changes in PaCO₂ (Kandel et al., 2013).

The level of respiratory chemosensitivity varies with developmental age, (Putnam et al., 2005) and once fully established it remains constant throughout the lifespan, at least in humans (Browne et al., 2003). Once in the extracellular fluid, CO₂ combines with water facilitated by carbonic anhydrase (CA) to produce bicarbonate ions and protons resulting in three possible acting chemosensory signals CO₂, and hydrogen (H⁺). For a number of years, the consensus was that CO₂ is detected entirely via its proxy, pH (Loeschcke, 1982). The effects of pH were initially deemed as extracellular, although now changes in intracellular pH (pHi) are known to be important. Although the term CO₂ chemosensitivity commonly refers to the detection of pH, it does not exclude other potential signalling molecules, the involvement of direct detection of CO₂ or has only recently gained attention. Different chemosensitive cells respond to different stimuli consequently due to the simultaneous adjustment of PaCO₂ and pH (Filosa et al., 2002; Hartzler et al. 2008; Huckstepp, Eason, Sachdev & Dale, 2010; Huckstepp, id Bihi et al., 2010; Mulkey et al., 2004; Wang et al., 2002). Huckstepp and Dale (2011) emphasised the importance of having a universal language in the cardiorespiratory physiology field to distinguish between pH chemosensitivity, bicarbonate chemosensitivity and CO₂ chemosensitivity as different chemosensitive cells respond accordingly to different stimuli.
Although modern neuroscience is making some advances, the identity of the primary sensory cells constituting central chemoreceptors and of their neuronal networks remain elusive. Neurons from many brain regions are excited or inhibited by CO$_2$/pH changes in vitro, which is in a controlled experimental environment rather than within a living organism or natural setting. Hence it has been difficult to link in vitro neuronal chemosensitivity to chemoreception in vivo, where investigations are carried out within a living organism or a natural environment. Furthermore, it is considered that central chemoreceptor locations are difficult to study, as they may also contain neurons with multiple functions that are not distinct from chemosensitive ones in their morphological or functional properties (Huckstepp & Dale 2011).

Quintero, Putnam and Cortovez (2018) in their study present an innovative ionic model that reproduces electrophysiological activity of CO$_2$/H$^+$ sensitive neurons located in the LC to study intrinsic chemosensitivity. Their findings highlight the potential to study altered chemosensitivity in a variety of disorders including PD.

### 3.2 PHYSIOLOGICAL ABNORMALITIES AND DISTURBANCES IN PANIC DISORDER

A number of environmental stressors including emotions, posture, alcohol, medications, weather and chemicals can disrupt normal breathing patterns. The most obvious symptom is usually the inability to breathe through the nose, comfortably, with the mouth closed. Hyperventilation is characterised as a form of mouth breathing. In consequence, the body’s response to hyperventilation is to restrict breathing, by increasing mucus secretions, inducing swelling in the nasal passages, tonsils and adenoids and result in spasm of the smooth muscle rings of the bronchi. Professor Buteyko infers that mouth breathing and hyperventilation can lead to a
number of health problems including asthma, chronic bronchitis, tonsilitis, sinusitis, rhinitis, and nasal polyps (Adelola, Oosthuiven & Fenton, 2013).

People who hyperventilate rapidly respond to any decrease in levels of CO₂ with increased respiration. Subsequently, levels of CO₂ are further depleted and increase respiratory symptoms. Disturbed breathing is often felt in the upper chest with overuse of the secondary muscles of respiration. Rapid upper chest breathing is typically observed during hyperventilation. Individuals who experience physical exertion during exercise report dizziness, palpitations, breathlessness, chest tightness, sudden fatigue, and many other symptoms, as a consequence of over breathing. Increased lactic acid production not only affects their fitness levels but increases hyperventilation. Low levels of CO₂ makes our nervous system more excitable. Brain wave patterns alter reflecting low uptake of O₂ as a result of the increased CO₂ levels (Martini et al., 2012). In summary, hyperventilation which is characterised by a feeling of suffocation is usually superseded by the need to maintain blood gas homeostasis, as even a small increase in CO₂ produces severe air hunger or dyspnea.

The respiratory control system is a fascinating example of a brain stem pattern that must be sufficiently stable to ensure survival yet flexible enough to accommodate a wide variety of adaptations (Kandel et al., 2013; Davies & Moores, 2003). The brainstem plays a crucial role in regulating homeostatic functions associated with PAs (i.e., chemoreception, cardio-respiratory control) (Gorman et al., 2000; Perna et al., 2014).

Neuroimaging studies conducted with PD patients have demonstrated that homeostatic pH disturbances play a role in panic physiology (Vollmer, Strawn, &
Sah, 2015). The nervous system’s function is to adapt and produce flexible behavioural responses to a changing environment. The brain’s highly adaptive defensive system reacts to threatening stimuli (e.g., predator, aversive stimulus) through generating rapid autonomic and behavioural responses (Maren, 2009). These behaviours are essential to survival and include securing food, shelter, water and most importantly, defending against immediate and perceived threats (Maren, 2009).

Evidence suggests that expected PAs are triggered in response to external triggers also known as exteroceptive threats (e.g., elevators, shopping malls). While, interoceptive threats such as an imbalance of acid-base and related pH chemosensory mechanisms are amongst some of the most significant internal homeostatic triggers responsible for the pathogenesis of spontaneous PAs (Vollmer et al., 2015). Acid-sensitivity serves differing functions (e.g., respiration, arousal, emotions) and is present across a range of brain regions that detects changes/disturbances in brain pH homeostasis, and depending on the level of threat, this system triggers a variety of “primal” responses (e.g., breathlessness, panic) (Esquivel et al., 2009; Griez, et al., 2007; Liotti, et al., 2001).

Respiratory sensations may also be affected by personality traits. Eysenck et al. (2007), proposed that the state of anxiety alters the executive functioning, which perpetuates and reinforces the appraisal of threat by the anxiety sufferer, thereby maintaining the reduced inhibitory functioning in the pre-frontal cortex (PFC) region. According to Cherniack et al. (2001) individuals who vary with psychological characteristics like anxiety differ in the intensity of respiratory sensations (i.e., a person with intensifying anxiety experiences dyspnea which leads to increased
respiratory efforts). This appears to be in line with previous research (Pain, Biddle & Tiller, 1989; Rushford, Tiller & Pain, 1989) postulating that PD may be inherently linked to an unstable ANS mediated by cognitive distress. Pain et al. (1989) explain the respiratory abnormalities found in PD, as adaptive and aimed at managing a hypersensitive CO₂ chemoreceptor system. Known common panicogens, for example, CO₂ and lactate stimulate the respiratory system by causing hyperventilation and inducing panic symptoms. Catastrophic misinterpretations and misattributions (i.e., bodily sensations and loss of control) may contribute to the exaggeration of panic symptoms and contribute to the maintenance of PD (Pain et al., 1989).

### 3.2.1 Panic Disorder and hypersensitivity to Carbon Dioxide

Respiratory abnormalities are a physiological marker for PD (Hegel & Ferguson, 1997; Holt & Andrews, 1998; Rapee, Brown, Antony & Barlow, 1992, Van den Hout, et al., 1992; Wilhelm et al., 2001). Patients with PAs have been repeatedly observed to have a vulnerability to CO₂ inhalation (Bellodi & Perna, 1998; Freire & Nardi, 2012; Gorman et al., 1984, 1989; Griez et al., 1990; Nardi et al., 1999, 2000; Perna et al., 1995). Hypersensitivity to inhaled CO₂ is one of the common manifestations of these respiratory disturbances. Among some of the important findings are reduced arterial and end-tidal CO₂ level at rest (Papp, Martinez, Klein, Coplan & Gorman, 1995; Papp et al., 1989). Moreover increased variability in tidal volume and/or minute ventilation was observed in participants while awake in the laboratory (Gorman et al., 1988; Papp et al., 1993) while asleep in the laboratory (Stein et al., 1995) and asleep at home (Martinez et al., 1995). Other findings here included, minute ventilation during PAs experienced in a laboratory setting (Goetz et al., 1993), exaggerated brain blood flow (Gibbs, 1992) endogenous lactate responses
to room air hyperventilation (Dager et al., 1995) and hypersensitivity to the effects of inhaled CO₂ (Battaglia & Perna, 1995; Gorman et al., 1994; Griez et al., 1987; Sanderson & Wetzler, 1990). Papp et al. (1995) demonstrated in their study that panic individuals exhibited irregularities in respiratory rhythms as characterised by higher variance and lower correlations in respiratory rate and tidal volume as compared to normal controls.

According to CO₂ hypersensitivity theory of panic, when respiratory control nuclei are stimulated during CO₂ inhalation, dyspnea triggers a series of autonomic arousal symptoms. Other respiratory challenges commonly used in laboratory settings that induce panic include lactate, cholecystokinin (CCK) and caffeine (Papp et al., 1992). Some studies have found that patients with PD have significant physiological variations in response to breathing CO₂, compared to normal controls (Fishman, 1994; Gorman et al., 1988; Perna, Cocchi, Bertani, Arancio & Bellodi, 1995). Pain et al. (1988) found in their study that first-degree relatives of patients with PD who are themselves free of PAs nevertheless have heightened anxiety in response to the CO₂ challenge, suggesting that the abnormal CO₂ response could be a genetic trait phenomenon. Gorman et al. (1997) established in their study that CO₂ sensitivity in patients with PD can be reduced by anti-panic treatment such as antidepressant medication.

Interestingly Briggs, Stretch and Brandon (1993) identified the respiratory subtype of PD as characterised by PD sufferers with prominent respiratory symptoms. Kircanski et al. (2009) in their theoretical review use Ley’s classification criteria to identify the PD respiratory subtype. Ley (1992) proposed that patients need to have four of the following five symptoms to fulfil the criteria. The symptoms include
feelings of choking or smothering sensations, shortness of breath, chest pain or
discomfort, numbness and tingling and fear of dying. Patients in the respiratory
subgroup reportedly had more out of the blue PAs and responded better to
antidepressant medication such as imipramine. The other subgroup presented with
less prominent respiratory symptoms had more situational PAs and responded more
effectively to benzodiazepines such as alprazolam. Building on this notion Biber and
Alkin (1999) in their study found that the subgroup of PD patients with more
prominent respiratory symptoms were more sensitive to the CO₂ challenge test, had
been suffering from PD longer, reported more severe panic and phobic symptoms, and
were more likely to be heavier smokers than patients with non-respiratory symptoms
(Freire & Nardi, 2012). Furthermore, it has been suggested that there is an altered
level of CO₂ sensitivity in the respiratory PD subtype in response to panic provocation
challenges including the CO₂ challenge and breath-holding (Nardi et al., 2004; Nardi
et al., 2006; Sardinia, Freire, Zin & Nardi, 2009). Research to support a respiratory
abnormality in PD is compelling (Abelson et al., 2001; Caldirola, Bellodi, Cammino,
& Perna, 2004; Stein, Millar, Larsen & Kryger, 1995; Yeragani, Radhakrishna,
Tancer & Uhde, 2002) and suggests that PAs are partly the result of respiratory
abnormalities rather than fear and anxiety alone.

The inhalation of CO₂ is a useful paradigm to study panic/anxiety as it has
been established that breathing CO₂ triggers PAs in patients with PD (Drury, 1918;
Klein, 1993; Papp et al., 1993; Sanderson et al., 1989). PD patients demonstrate an
increased sensitivity to CO₂ inhalation (Papp et al., 1993; Rassovsky & Kushner,
2003; Rassovsky, Abrams & Kushner, 2006) and dysregulated brain pH (Friedman,
2006; Maddock, 2001). According to the CO₂ hypersensitivity theory, PD patients
have increased sensitivity of their chemical chemoreceptors (Klein, 1993). The “Suffocation False Alarm” (SFA) theory proposed by Klein (1993), suggests that PAs arise as a result of primitive defensive reactions to threats detected in the body’s internal environment, which is different to that of fear responses (Klein, 1993; Perna et al., 2014).

Klein (1993), postulated that activation of phylogenetically primitive brain regions that include the brainstem areas may be associated with unexpected PAs, while higher brain systems may be related to anticipatory and/or phobic avoidance (Damasio, 2000). Although a disadvantage to Klein’s model of the suffocation false alarm (SFA) system, is that anatomically or functionally no structure has been located within the CNS. The best candidates to fulfil the function of a suffocation monitor are the CNS structures linked to chemosensitive properties and the fear circuitry involved in PD (Freire & Nardi, 2012). These areas are incorporated in the broad brainstem respiratory network and include the nucleus tractus solitarii, the locus coeruleus, and the raphe nuclei (Gorman et al., 2000; Griez & Perna, 2003).
3.2.2 Carbon Dioxide and its role in Chemosensation

CO₂ is constantly produced in the body as a result of end-product carbohydrate metabolism and is processed by the bicarbonate system (Esquivel et al., 2009). CO₂ and water interact to form carbonic acid (H₂CO₃), and the effect of CO₂ on brain tissue is facilitated by parallel increases in H⁺ ions that are present as a result of dissociation of H₂CO₃, which plays a vital role in the bicarbonate buffer system aimed at maintaining acid-base homeostasis (Cadoux-Hudson et al., 1990; Esquivel et al., 2009; Jensen et al., 1988; Martoft et al., 2003).

Inhaling high concentrations of CO₂ leads to a decrease in pH and an increase in H⁺ across the blood-brain barrier and in body fluid compartments, which results in respiratory acidosis (Esquivel et al., 2009). Increasing levels of CO₂/H⁺ induces dramatic physiological responses that serve as an adaptive panic/defence response and include neuroendocrine, autonomic and behavioural responses (Johnson et al., 2011). The blood-brain barrier is permeable to CO₂ allowing variations in partial pressure of CO₂ (PaCO₂) to influence brain pH. Once CO₂ permeates the blood-brain barrier, the resulting HCO₃⁻ and H⁺ of hydrolysed CO₂ leads to temporary acidification of extracellular brain fluids (Battaglia, 2017; Guyunet, 2014). When CO₂ levels in the body increase, a process mediated by CO₂/H⁺ peripheral and central chemoreceptors, ventilatory stimulation is subsequently elicited (Esquivel et al., 2009). Increased ventilation to restore pH and partial pressure of oxygen (PaO₂), increased arousal, and anxiety are some responses through which mammals react to increased acidification (Battaglia, 2017).
According to Richerson (2004), serotonin-producing cells in the raphe nuclei have been recognised as CO₂ sensors and are thought to form the cellular link between serotonin, chemoreception and panic. The serotonergic raphe neurons located in the brain stem behave as pH regulators and are responsible for detecting decreases in pH due to hypercapnia, and respond with stringent mechanisms such as autonomic and behavioural responses to preserve pH homeostasis. These serotonergic neurons which are strategically based near the large arteries to detect CO₂ levels rising in the blood have projections to the anterior limbic and pre-frontal fear processing circuits and are implicated in the panic-like responses of CO₂ (Severson, Wing, Pieribone, Dohle & Richerson, 2003). Buchanan and Richerson (2009) found that when pH sensitive serotonergic neurons are silenced in mice, they disrupt chemosensitive responses to CO₂ inhalation, which impairs respiration.

Canteras and Graeff (2014), implicate that faulty serotonergic inhibition of the DPAG and deficits in the autonomic medullary centres pose a vulnerability to PAs. This in their view, may be associated with faulty opioid buffering mechanisms since serotonin and opioids have been demonstrated to interact in the DPAG. Evidence suggests that patients suffering from PD are more likely to experience PAs due to the lack of effective 5-HT inhibition of neural networks that “integrate defensive reactions to proximal danger” and an oversensitive suffocation false alarm system, coupled with defective buffering of endogenous opioids (Graeff, 2012; Graeff, 2017). Recently it was found that 5-HT interacts with endogenous opioids in the DPAG (the structure that is vital for regulating PAs and proximal defence) (Graeff, 2012; Graeff, 2017). PD patients are likely to experience panic symptoms when they inhale a single deep breath of CO₂ as it stimulates the hypersensitive respiratory control nuclei,
producing a subjective sense of dyspnea, which in turn triggers typical autonomic symptoms (i.e., elevated heart rate) identified by PD patients as panic (Muhtz et al., 2011; Verburg et al., 1998).

The nucleus tractus solitary, the medullary raphe, the locus coeruleus, the nucleus ambiguous, and the ventrolateral medulla are brain regions that play a role in ventilation and that have been found to contain CO₂/H⁺ sensitive neurons (Equivel et al., 2009; Putnam et al., 2004). Neurons sensitive to increases in levels of CO₂ and H⁺ multiply their rate of firing in response to detecting increased acid in the brain (decreased pHᵢ) increased CO₂, and/or decreased extracellular pH (Esquivel et al., 2009; Putnam et al., 2004). They also demonstrate a consistent reduction in pHᵢ during increased extracellular acid load (Esquivel et al., 2009; Putnam, 2001). Furthermore, pH-sensitive ion channels mediate chemosensitive signalling and sensitivity to acid (Esquivel et al., 2009). Esquivel et al. (2009) suggests that an overlap exists between chemosensitive neurons that play a role in respiration and neurons that provoke panic, as patients with PD, especially those that experience spontaneous PAs, commonly experience respiratory symptoms (Briggs, et al., 1993; Colasanti et al., 2008; Schruers et al., 2004). It has been suggested that brain regions containing CO₂/H⁺- sensitive neurons, such as the LC and hypothalamus, are responsible for respiratory actions and autonomic defensive responses (Bailey et al., 2003; Equivel et al., 2009; Putnam et al., 2004; Williams et al., 2007).

Evidence suggests PAs may be the result of abnormal respiratory regulation and/or over sensitivity of the central neural network of CO₂/H⁺ chemoreception
Diaphragmatic changes have been noted in both disrupted and dysregulated breathing patterns. When a fight/flight response is activated, rapid, shallow and thoracic breathing dominates where high levels of tonic contraction of respiratory muscles expand a lot of energy and homeostatic functions needed for repair and renewal are impaired (Courtney, 2009).

Inhalations of CO₂ can be life-threatening, hence why they initiate a fear response that requires sensitive detection and action to ensure survival. Panicogenic and anxiogenic effects induced by CO₂ inhalations and evidence of hypersensitivity to CO₂ both point to a molecular and anatomical structure which acts as a chemosensor that detects threats posed by CO₂ and responds to these by activation of the SNS and the fight and flight response (Muhtz et al., 2011).

The subject of CO₂ chemosensitivity has developed considerably in recent years. Central chemoreceptors play an important role in cardiorespiratory homeostasis. One common mechanism for chemosensitivity is the direct activation of ion channels by a drop in extracellular pH levels. The gating of many ion channels is modulated by large changes in extracellular proton concentration (Hille, 2001).

Panic patients are considered to be on one end of the spectrum with high sensitivity to rising CO₂ levels, whereas on the other end of the spectrum, those that have very low sensitivity to CO₂ include individuals suffering from congenital central hypoventilation syndrome and divers (Harper et al., 2005; Delapille et al., 2001).
This led Harper et al. (2005) to believe that the central hypoventilation syndrome may be the pathophysiological mirror picture of PD. Breath-hold (BH) divers have a lower ventilatory response to CO₂, which has been related to diving experience (Delahoche et al., 2004).

Elite BH divers exhibit higher anaerobic metabolism (Ferretti, 2001) and physiological adjustments to apnea that lead to lower acidosis (Joulia et al., 2002). Joulia et al. (2003), found that repeated exposure to extended BHT increases the body’s production of endogenous antioxidants. This, in turn, raises the anaerobic threshold and the capacity to exercise at increased levels of exertion. A possible explanation for this may be that given that the marker for breathing is the CO₂ build-up rather than the starvation of O₂, BH athletes have developed trained effects and can endure and tolerate a lot more CO₂ build-up in the blood and tissues before they need to take another breath). As described previously, respiratory control is very sensitive to changes in PaCO₂. The build-up of CO₂ and lactic acid during prolonged apnea results in progressive acidosis (Olsen, Fanestil, & Scholander, 1962). It is the increases in PaCO₂ that stimulate the central chemoreceptors in the brain, leading to an increase in ventilation thus decreasing PaCO₂ (Wood, 2012).

The DR has been observed to be more powerful in divers than in those of untrained individuals, suggesting that divers are likely to store more lactate in underperfused tissues (Rodriguez-Zamora et al., 2018; Schagatay & Andersson, 1998). Correspondingly, Joulia, Steinberg, Gavarry and James (2002), obtained lower blood lactate levels in trained divers compared to their non-diver counterparts following resting or working apneas and also following eupneic exercise. It is unclear
whether these differences were induced by the diving training, but remarkably it was noted that the non-divers had lower lactate accumulation after hand grip exercise with apnea than without apnea. Although lactate is a common panicogenic that induces panic attacks in individuals suffering from PD, in free divers it appears that they are able to withstand more of a tolerance given that they are likely to accumulate more lactate in underperfused tissues as a result of anaerobic metabolism. Schagatay (2009) speculated that one of the necessary features for enduring prolonged apnea may be the blood-buffering capacity for hydrogen ions from accumulating CO₂ and lactic acid. It is thought that the increased haemoglobin (Hb) resulting from apnea training may lead to a number of changes, including increase of buffering capacity, splenic contraction to add to this effect, and lung-volume expansion which has a diluting effect on CO₂ (Schagatay, 2009). Ferretti (2001) proposed that the overall CO₂ storage in divers was estimated to be twice that of non-divers. Schagatay (2009) suggested, that this notion referred to as “lactate paradox of apnea” is of interest and needs to be further researched with this unique group, that of free divers.

### 3.3 RESPIRATORY PROVOCATION TESTS

#### 3.3.1 Carbon Dioxide (CO₂)

Respiratory provocation tests have been fruitful in generating hypotheses about panic disorder (PD). A common respiratory test is the 35% CO₂ challenge which involves taking one single deep inhalation of a gas mixture containing 35% CO₂ and 65% O₂ or double breath inhalations. Under these conditions, healthy individuals develop a brief respiratory response accompanied by neurovegetative symptoms that largely overlap with symptoms commonly experienced during a panic attack (PA) (Griez & Van den Hout, 1982; Nardi, Freire & Zin, 2009; Van den Hout
& Griez, 1984). In individuals who suffer from PD, the CO₂ challenge induces a sharp and transitory rise in anxiety symptoms that have been compared to having a PA (Griez et al., 1987; Nardi, Valenca, Nascimento, Mezzasalma & Zin, 2000; Perna, Battaglia et al., 1994). Administered in a controlled laboratory setting, the 35% CO₂ challenge is a brief test whose effects are completely vanished within seconds (Griez, & van den Hout, 1982). Repeated studies have demonstrated that the 35% CO₂ challenge is considered to be a safe and non-invasive procedure, devoid of unwanted consequences both in short and long terms (Nardi et al., 2007; Perna, Cocchi, Allevi, Bussi, & Bellodi, 1994). The CO₂ challenge strongly suggests a relationship between the pathophysiology of PD and breathing or respiratory disturbances. Some abnormalities in respiration, such as enhanced CO₂ sensitivity, have been observed in individuals who suffer from PD. Muhtz et al. (2011), demonstrated in their study that inhalation of a deep breath of 35% CO₂ produced significant panicogenic and anxiogenic effects in patients suffering from disorders such as PTSD and PD, in which the fear centres and circuitry of the brain are involved. Previous studies suggest common pathological processes in the noradrogenic / locus coeruleus system in patients with PTSD and PD (Bailey, Argyropoulos, Lightman, & Nutt, 2003). A study by Grillon et al. (2008) demonstrated that PTSD and PD patients have an increased fear-potentiated startle response in an unpredictable aversive context as opposed to a predictable situation when compared to healthy individuals. In a more recent study, Grillon et al. (2017) identified that individuals with PAs demonstrated hypersensitivity to unpredictable threatening situations. It has also been suggested that common pathological processes in the noradrogenic / locus coeruleus system exist in patients with PTSD and PD (Bailey, Argyropoulos, Lightman & Nutt, 2003; Charney & Heninger, 1986; Charney et al., 1992).
3.3.2 Hyperventilation

Hyperventilation has been reflected upon by researchers as a cause, correlate and a consequence to panic attacks (PAs) and it has been studied extensively in PD in comparison with other diagnoses (Nardi, Valenca, Nascimento & Zin, 2001; Papp, Klein, & Gorman, 1998). Some authors support the causal relationship of hyperventilation playing a key role in the development of PAs.

It is regarded that chronic hyperventilation in PD patients shifts to hypocapnic alkalosis as a consequence of stress or anxiety induced acute hyperventilation thus resulting in PAs. Freire and Nardi (2012) postulate that this hypothesis has been formed based on three experimental pieces of evidence. First PAs and the hyperventilation syndrome share common symptoms which include dyspnea, palpitations, tremors, paresthesias and faintness. Second, the hyperventilation syndrome has been reportedly overlapping with PD in 40% of patients (Nardi et al., 2001). Third, the hyperventilation challenge test induces panic like symptoms in a significant percentage of PD patients (Garssen, Van & Bloemink, 1983; Nardi et al., 2004). Other respiratory challenges have included hyperventilation which involves breathing fast and shallow and averaging approximately 30 breaths per minute. This causes a significant drop in end-tidal CO₂ (exhaled carbon dioxide) to conventionally accepted levels of hypocapnia.

3.3.3 Breath-holding

Another common respiratory test to induce endogenous CO₂ is breath-holding, which is considered to be a natural and simple method (Van Der Does, 1997). Studies that have utilised the breath-holding challenge to investigate panic have yielded
mixed results. Zandbergen, Strahm, Pols and Griëz (1992) examined whether breath-holding durations can be used to diagnose panic disorder (PD). They established that PD individuals in their study had shorter BH durations than normal individuals, however similar to those of other anxiety disorders.

Asmundson and Stein (1994) in their study reported that patients diagnosed with PD had significantly shorter BH durations relative to healthy participants as well as participants suffering from social anxiety disorder. These findings are in line with Klein’s (1993) theory of the suffocation false alarm (SFA) theory. Asmundson and Stein (1994) suggest that PD participants terminate the breath-hold earlier in order to avoid activation of the suffocation alarm. Freire and Nardi (2012), have hypothesised that there is an integral abnormality in the physiological mechanisms that control respiration in PD. In response to many of the common used respiratory challenge tests, including the CO₂ challenge, hyperventilation and breath-holding, PD patients exhibit physiological and behavioural abnormal responses. They often report more PAs and anxiety during respiratory challenges when compared to normal healthy individuals (Gorman et al., 1994; Holt & Andrews, 1989; Papp et al., 1997).

Furthermore, it has been found that the respiratory group subtype is sensitive to the BH challenge (Nardi, Valenca, Lopes, Nascimento & Mezzasalma, 2004; Nardi, et al., 2006; Nardi, Valenca et al., 2006).
3.4 IMPLICATIONS OF THE DIVING RESPONSE IN TREATING PANIC DISORDER

Respiratory abnormalities and cardiovascular problems can be quite common in patients suffering from PD, and many of the symptoms have an overlap with such disturbances. Multiple susceptibility genes and their interplay with environmental factors as well as chemosensitivity have been understood to play a significant role in the aetiology of PD. A number of empirically supported risk factors for PD have been identified and extend multiple levels of function including genetic, biological and psychosocial factors (Feldner et al. 2008; Zvolensky et al. 2006c). Although advances and developments in the neurobiology of PD may be able to offer new opportunities towards the treatment and prevention of PD, a greater understanding is required of the link between respiratory abnormalities and PD. Particularly, comprehending the mechanisms of chemosensation involved in respiration, and the role that acid-sensing ion channels and tandem acid sensitive potassium channels play in disrupting the homeostatic tight parameters of the brain pH levels may shed some light in understanding the PD and its link with chemosensation. Indisputably, PD has a very complex pathophysiology, and hence further research is required in understanding what role pH regulation and pH-sensitive receptors play in its onset and maintenance of symptoms. In view, understanding the molecular and cellular biological and genetic influences involved in PD is fundamentally important in gaining further insights. PD has been pivotal in research dealing with the respiratory system and anxiety disorders (Gorman, Kent, Sullivan & Coplan, 2000a).

There is converging evidence from neuroimaging, genetic and animal studies that support that respiratory provocation tests such as the CO₂ challenge,
hyperventilation and BH challenge disrupt pH homeostasis regulation, and underlying abnormalities in chemosensation may play a role in panicogenesis. Specifically, acid-chemosensory mechanisms involved in the fear circuitry may evoke fear and panic responses to interoceptive stimuli resultant from respiratory provocation methods (Vollmer et al., 2015). Hence, restoring the homeostasis regulatory mechanisms within the interoceptive milieu may be the key to managing panic symptoms. Correcting dysfunctional breathing has often been used to restore the balance in the neurovegetative system however this has yielded mixed results (Wilhelm et al., 2001).

Although CBT is considered to be the most effective treatment modality proposed to date for anxiety disorders, it is still far from optimal (Craske et al., 2014; Hofmann & Smits, 2008). In the last few decades, neuroscience has contributed vastly to our understanding of the human brain and psychological and biological treatments have been influenced by developments in neuroscience. Kindt (2014) argues that a neuroscientific approach can contribute to our understanding regarding the mechanisms of change in the treatment of pathological anxiety and processes involved in how one individual develops abnormal fear that stems from having normal adaptive fear. Associative fear memory purportedly lies at the core of anxiety and associated disorders (e.g., PD, PTSD, specific phobia), and given that the fear circuitry is involved in the pathophysiology of PD, neurobiological and neuroscientific research can complement cognitive behavioural treatment.

MacLean (1990) developed a groundbreaking theory of understanding brain development called the “triune brain”. The triune brain is a model of development which encompasses the reptilian complex, the paleomammalian complex and the
neomammalian complex. MacLean contended that the reptilian brain is the first to develop and is responsible for regulating automatic voluntary functions that are vital for survival, including heart rate, breathing, blood pressure, and body temperature regulation. It also handles motor planning and basic effects including physiological aspects of aggression and anxiety. It comprises the brainstem, pons and diencephalon (Kandel et al., 2013).

MacLean (1990) postulated that the paleomammalian complex, which houses our emotions and is important for social emotions and expanded memory functions, consists of the amygdala, hippocampus, thalamus, hypothalamus, septum and cingulate cortex. MacLean termed this area as the limbic area and indicated that these structures develop sequentially following the development of the reptilian complex. The neomammalian complex which consists of the cerebral cortex, also known as the neo-cortex is only found in mammals. MacLean (1990) maintained that in human evolution, this is the most recent step conferring the ability for language, perception, abstract cognitive processes, and sequential planning and organising. The neocortex receives the most influence from its environment and is more adaptable and malleable. Although to date there have been more sophisticated models put forward explaining brain functioning, MacLean’s ideas have had a profound effect in understanding the sequential pathogenesis of anxiety disorders and feared responses in individuals (Newman, 2009).

Evolutionary pressures, and the driving motivations of any organism to survive explains the need to maximise pleasure and minimise harm (Gordon et al. 2007; Öhman & Mineka, 2001). Therefore, stimuli such as the threat of CO₂ that has
been linked through evolution to danger are particularly salient (Kavaleris & Choleris, 2001; Lang & Davis, 2006). Moreover, threats can arise from within the organism and can include detectable changes within the interoceptive milieu (Esquivel et al. 2010; McNaughton, 1989), cognitive misappraisals (Barlow, 2002), and imagined threats (Bremmer, 2004).

It is commonly recognised that when an individual panics, the fear is described as so imminent that a person cannot think clearly, nor challenge their thoughts and it is because this fear is so prominent that it is quickly paired with interoceptive and exteroceptive stimuli. The acceleration of the heart rate, or the pounding of the heart is often one of the scariest symptoms reported by panic patients and because the fear is so imminent, it is commonly misinterpreted as a sign that one is having a heart attack. Furthermore, choking sensations and dyspnea are often misattributed to suffocation.

Current exposure-based therapies are amongst the most popular and most effective treatments for anxiety disorders aimed to reduce pathological fear. According to Milad, Rosenbaum and Simon (2014), anxiety and trauma interventions can be further improved by having a deeper understanding of the neurobiological mechanisms of fear extinction to enhance initial and long-term outcomes. Mineka and Zinbarg, (2006) proposed that the genesis of irrational fears originates from an association between neutral and aversive stimuli. Hence, it may be imperative to know that insight in the neurobiology of associative fear memory may contribute to our understanding of the mechanisms of change in the treatment of anxiety and other
related disorders (Hermans, Craske, Mineka & Lovibond, 2006; Kindt, 2014; Milad, Rauch Pitman & Quirk, 2006).

Given MacLean’s (1990) and Newman’s (2009) ideas, based on the triune model of the human brain evolution and recent neuroscientific advances in this fast growing area, there is a need for science to develop simple treatments that employ a bottom-up approach, where safety and primary needs are met prior to engaging in cognitive interventions. During a state of panic, when experiencing exaggerated fear, it is difficult to think rationally and hence challenge one’s irrational thinking. Based on this assumption that these needs are initially met, one is then able to access cognitive capacity and engage in cognitive restructuring more effectively. Neurobiological insights support psychotherapeutic interventions that focus on providing a supportive therapeutic environment that facilitates the safety needs of the patient by prioritizing the stabilization of the autonomic nervous system when dysregulated (Furmark et al. 2002; Grawe, 2007; LeDoux, 2002; Merzenich, 1983; Newman, 2009; Rothschild, 2017; Sporns, 2011). One of the cardinal features of PD when fear is elicited is a dysregulated ANS, characterised by sympathetic nervous system (SNS) arousal. Many PD patients complain of heart palpitations or chest pounding which are perceived as dangerous and which exaggerate their fear response. One may anticipate that by reversing the accelerated heart rate and consequently the SNS arousal, panic patients may be able to achieve stabilisation and increase their perceived sense of safety and control. PD patients may be able to benefit from simple and practical treatments aimed at regulating the ANS and reversing the fear response.
One such strategy may be to activate the diving response (DR), the most powerful autonomic reflex known to humans, which consequently reduces the heart rate and initiates parasympathetic nervous system responses. Moreover, if stabilisation is effectively achieved by reversing the accelerated heart rate and stopping the palpitations, panic patients may benefit from repeated exposures of simple practical strategies which activate the DR. Activating such an innate powerful response, may down regulate the fear or panic response and prove to be an effective novel treatment for PD. Furthermore, regular activation of the DR may assist with unpairing aversive fear conditioned responses such as interoceptive and exteroceptive stimuli. One known strategy that activates the DR, is the cold facial immersion (CFI) which is routinely used in emergency departments for the treatment of atrial tachycardia, to reset the elevated heart rate. The CFI task successfully activates parasympathetic nervous system responses and slows down the heart rate considerably.

According to Andersson & Schagatay (1998), frequent and extensive exposures to hypercapnia (high CO₂ levels in the blood) may reduce the sensitivity of the central chemoreceptors, thereby reducing the urge to breathe which is stimulated by hypercapnia. Furthermore, Andersson and Schagatay (1998) postulated that future studies should investigate the time course for development of this adaptation to breath-hold (BH), cold facial immersion (CFI) and or diving, (i.e., how many exposures and how frequent exposures are needed to reduce CO₂ sensitivity). As discussed earlier, the training effects that free divers possess may be beneficial for individuals suffering from panic attacks (PAs). Walterspacher, Scholz, Tetzlaff and Sorichter (2011) proposed that one’s response to CO₂ is largely determined by
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genetics and apnea training. Particularly, repetitive breath-hold (BH) training with short recovery interval periods, have also demonstrated to increase the time in withstanding the respiratory drive, and diminishing the ventilatory response to hypercapnia, contributing to longer BH times (Schagatay et al., 1999).

In many ways, the physiological adaptations experienced whilst free diving are the opposite of those triggered when an individual encounters a panic attack. Free diving has been described as the feeling of “true ease and relaxation” under the water. However, given the extreme nature of the sport, it is unlikely that individual’s with PD would engage in free diving. Despite this, some of the techniques and physiological adaptations used in free diving may be easily taught to PD patients and utilised to counteract panic symptomatology. These may include breath-hold training (BHT) and regular practice of the CFI task. Given that the key factors in both free diving and PAs are mental and breathing control, it is plausible that the diaphragmatic breathing techniques already used to treat panic may benefit from drawing on the physiological adaptions and techniques used in the sport of free diving and in particular the activation of the DR.
3.5 RESEARCH AIMS

The overarching aims of this research are to examine the efficacy of cold facial immersion and the diving response in treating panic disorder. Whilst the diving response and cold facial immersion has been used in medical applications (i.e. treatment of atrial tachycardia), this study is the first attempt to examine applications of the diving response and cold facial immersion to treat panic symptoms.

As a preliminary investigation, this research examined the immediate effects of apnea (breath-holding) and cold facial immersion on panic symptoms and cognition. This preliminary study aims to examine the short-term effects of CFI on physical and psychological symptoms of panic and examine differences between individuals with panic compared with individuals healthy control participants.

Based on the findings of this literature review it was predicted:

1. That clinical participants will have shorter breath-hold durations than healthy controls in both breath-hold challenges, in line with Klein’s suffocation false alarm hypothesis.

2. That clinical and control participants will experience a heart rate reduction in response to the cold facial immersion (CFI) tasks, given the activation of the DR. Furthermore, it is predicted that there will be no significant difference in heart rate reduction between clinical and control participants.

3. That clinical participants will demonstrate increased heart rate and respiration rate in response to the CO₂ challenges when compared to control participants.
4. That clinical participants will report increased anxiety-related symptoms when compared to control participants, in response to the CO₂ challenge.

5. That all participants will report significantly lower anxiety in response to the CO₂ challenge with Cold Facial Immersion when compared to baseline measures and the CO₂ challenge alone.
Chapter 4

OVERALL METHODOLOGY

4.1 OVERVIEW OF METHODOLOGY

This chapter presents the overall methodology of the research conducted for this thesis. The research studies are presented as three individual studies in the following chapters (Chapters 5 – 7). As each of the chapters of these studies provides a Method section which outlines methodological aspects that are relevant to each of the studies, procedures and statistical analyses), the methodology which will be described in this chapter is restricted to the elements that are common across all of the studies.

4.2 ETHICS APPROVAL

Approval for this research was obtained from the Swinburne University Human Research Ethics Committee (SUHREC 2014/010) on February 14th 2014. Ethics was granted to conduct two studies: (1) preliminary study, and (2) an investigation of the effects of cold facial immersion (CFI) on CO₂ sensitivity. Both of these studies were to be conducted with clinical participants, diagnosed with panic disorder, and a group of healthy control participants. The initial design for the preliminary investigation included a homework intervention whereby all participants would practice three CFI tasks daily over a period of four weeks. The initial design for the investigation of the effects of CFI on CO₂ sensitivity included a comparison of a six week CFI intervention (conducted at home by participants) with a six week
online Cognitive Behavioural Therapy, where participants would be randomly assigned to interventions. However, due to ethical and safety considerations with regard to participant’s carrying out CFI tasks in their home, in a standardised and supervised way, this original research design was not granted ethics approval. Hence methodology for both the preliminary study and subsequent study investigating CFI and its effects on CO₂ was changed and ethics approval was granted for the research which is reported in this thesis.

Throughout this research, amendments to ethics have been made in regards to exclusion criteria, the location of the research, supervisory arrangements, changes to the research protocol, and extension of the ethics approval period (see Appendix A for ethics approvals and approved amendments granted by SUHREC 2014/010).

4.3 INFORMED CONSENT

As clinical and control participant groups underwent slightly different screening procedures, they were provided with different Plain Language Statements (PLS) and Consent Forms (see Appendix B and C for copies of the Plain Language Statement and Consent Form for clinical and control participants for the two studies conducted as part of this research). The PLS and consent forms outlined the aims and requirements of the research study and provided participants with information regarding their rights as research participants. These forms also provided information regarding contact details for participants to contact should they require any further information or have concerns about the research.
Upon expressing interest in participating in the research, participants were invited to a preliminary health screening and clinical interview. Prior to the commencement of the health screening and clinical interview, participants were provided with the PLS and consent form and asked to provide consent by completing and signing the form. Following the consent process, the health screening and clinical interview commenced.

4.4 CLINICAL PARTICIPANTS

4.4.1 Inclusion and Exclusion Criteria for participants with panic disorder.

The key inclusion criterion for clinical participants was a primary diagnosis of panic disorder with or without agoraphobia, according to the diagnostic criteria of DSM-5 (APA, 2013). Participants who were using prescription medication, including antidepressants and benzodiazepines were excluded from the study. Participants with a first-degree biological relative with panic disorder were also excluded. Other exclusion criteria for clinical participants included: a diagnosis of comorbidities to Axis I mental health disorders according to the diagnostic criteria of DSM-5 (APA, 2013), psychotic disorders, substance abuse, known allergies to latex, asthma or respiratory problems, cardiovascular problems, hypertension, hypotension, pregnancy, and cerebrovascular problems including epilepsy, and organic brain disorder. In summary, the inclusion and exclusion criteria were selected based on the medical risks in relation to the CO₂ challenge and our attempts to recruit a homogeneous sample in order to reduce confounders.
4.4.2 Recruitment of Clinical Participants

Clinical participants were recruited from a range of clinical and community settings. Clinical sources included referrals from psychologists across three large private psychology clinics based in Melbourne. Community sources included referrals and self-referrals made by members of community based organisations such as the Anxiety Disorders Association of Victoria, (ADAVIC), and the Anxiety Recovery Centre Victoria (ARCvic). The study was predominantly advertised at these locations as well through online social media platforms connected with these organisations, as well as a neuropsychotherapy e-journal, a Melbourne based newspaper, and at Swinburne University medical clinic and around the university campus.

Potential participants who applied to participate in the study were invited to undergo a clinical screening interview conducted by the principal researcher at Swinburne University. Screening interviews ranged in duration from 40 minutes to 60 minutes. During the screening interview, the researcher provided potential participants with information regarding the study. Health screening assessments were carried out to establish medical eligibility to undergo the CO₂ challenge. As part of the health screening, all participants completed a demographic and health information form (see Appendix D for Participant Information Form). Demographical data such as age, gender, level of education completed, employment status were included in this form. In addition, the demographical questionnaire included a health screening, height and weight information, as well as fitness and exercise assessment which included a physical activity index. Participants were also asked about their perceived level of comfort with water.
Furthermore, all participants were administered The Mini International Neuropsychiatric Interview (M.I.N.I). The M.I.N.I is a short structured diagnostic interview used to make diagnoses of Axis I disorders (DSM-IV) and has demonstrated high reliability and validity (Sheehan, et al., 1997). The 5.0 version of the M.I.N.I schedule was used to screen psychological disorders within the exclusion criteria and identify individuals with PD (DSM-IV). Clinical participants were also assessed with the structured clinical interview (SCID-I) for DSM-IV Axis I Disorders (SCID-I; First, Spitzer, Gibbon & Williams, 1995) module for Panic Disorder and Agoraphobia in order to confirm the diagnosis. The diagnostic assessment was conducted by the researcher who is a clinical psychologist. The SCID-I is a comprehensive structured interview that assesses for current episodes of anxiety disorders and allows differential diagnosis among the DSM-IV anxiety disorders (First, Spitzer, Gibbon, Williams, 1996). The SCID-I has demonstrated a high level of reliability (e.g., Kappas of at least .75 on symptoms and 90% accuracy in diagnosis) (Ventura, 1998). Validity has been demonstrated via a number of studies that have used the SCID-I as the “gold standard” in determining the accuracy of clinical diagnoses (e.g., Shear et al., 2000; Steiner et al., 1995).

4.5 CONTROL PARTICIPANTS

4.5.1 Inclusion and Exclusion Criteria for Control Participants.

The key inclusion criterion for control participants was a negative diagnosis of panic disorder or other mental illness, according to the diagnostic criteria of DSM-5 (APA, 2013). As per the exclusion criteria for clinical participants, control participants who were using prescription medication, including antidepressants and benzodiazepines were excluded from the study. Control participants with a first-
degree biological relative with panic disorder were also excluded. Other exclusion criteria for control participants included: a diagnosis of comorbidities to Axis I mental health disorders according to the diagnostic criteria of DSM-V (APA, 2013), psychotic disorders, substance abuse, known allergies to latex, asthma or respiratory problems, cardiovascular problems, hypertension, hypotension, pregnancy, and cerebrovascular problems including epilepsy, and organic brain disorder. In summary, the inclusion and exclusion criteria were selected based on the medical risks in relation to the CO2 challenge and our attempts to recruit a homogeneous sample in order to reduce confounders.

### 4.5.2 Recruitment of Control Participants

The control participants in this study were recruited from various sources and predominantly through snowball techniques through the researcher’s contacts through Swinburne University and private practice settings. Social media platforms were also used to advertise the research and attract control participants as well as advertising on research notice boards throughout Swinburne University. Figure 5 depicts the process of recruiting participants for this research study.
As per the screening procedure for the clinical participants, potential control participants who applied to partake in the study were invited to undergo a clinical screening interview conducted by the principal researcher at Swinburne University. Screening interviews ranged in duration from 30 minutes to 45 minutes. The screening process for control participants was not as long as it was for the clinical participants.
participants. During the screening interview, the researcher provided potential participants with information regarding the study. Health screening assessments were carried out to establish medical eligibility to undergo the CO$_2$ challenge. As part of the health screening, all participants completed a demographic and health information form (see Appendix D for Participant Information Form). Demographical data such as age, gender, level of education completed, employment status were included in this form. In addition, the demographical questionnaire included a health screening, height and weight information, as well as fitness and exercise assessment which included a physical activity index (PAI). Participants were also asked about their perceived level of comfort with water.

Furthermore, participants were administered the Mini International Neuropsychiatric Interview (M.I.N.I). The 5.0 version of the M.I.N.I schedule was used to screen psychological disorders within the exclusion criteria and identify individuals who did not meet the diagnostic criteria for PD or any other mental illness according to the DSM-IV (APA, 2013).

4.6 OVERALL PROCEDURE

The following measures relate to the two quantitative studies reported in chapter 5 and 6 respectively and include (1) Psychological Measures, (2) Physiological Measures (3) CO$_2$ Challenge, (4) Breath-hold challenge (5) Cold Facial Immersion (CFI) Task. All participants completed the psychological measures as well as the CO$_2$ Challenge, Breath-hold challenge and CFI Task. These conditions are discussed below.
4.6.1 Psychological Measures

As part of the experimental procedure, all participants completed a battery of psychological measures which comprised a number of self-report measures. The battery of tests was administered a number of times throughout the experimental studies. Chapters 5 and 6 provide further detail regarding the administration of this battery of measures throughout the experimental process.

4.6.1.1 The Anxiety Sensitivity Index

Anxiety sensitivity was measured using the Anxiety Sensitivity Index (ASI). The ASI is a 16-item self-report questionnaire that is designed to measure the construct of anxiety sensitivity, which is defined as the tendency to fear the possible consequences of somatic and cognitive anxiety symptoms (Peterson & Reiss, 1987). Examples of the items include, “It scares me when my heart beats rapidly” and “It scares me when I am short of breath”. The items of the ASI are rated on a 5-point Likert scale ranging from 0 (very little) to 4 (very much). The ASI has demonstrated adequate internal consistency (Telch, Shermis and Lucas, 1989) and test-retest reliability (Mailer & Reiss, 1992). Moreover, the ASI appears to measure fear of anxiety symptoms as opposed to state or trait anxiety (see McNally, 1994).

4.6.1.2 The Beck Anxiety Inventory

To measure overall anxiety, the Beck Anxiety Inventory (BAI) was used. The BAI is a 21-item self-report questionnaire that assesses the degree that physical and cognitive anxiety symptoms have affected an individual over the past month (Beck, Epstein, Brown & Steer, 1988). Participants indicate the level to which they have been bothered by anxiety symptoms over the past month. Examples of the symptoms
measured include “Unable to relax”, “Numbness or tingling” and “Fear of losing control”. The BAI is rated on a Likert scale ranging from 0 (Not at all) to 3 (Severely, it bothered me a lot) and raw scores ranging from 0 to 63. BAI scores are classified into 4 categories including minimal anxiety (0 – 7), mild anxiety (8 – 15), moderate anxiety (16 – 25) and severe anxiety (30 – 63). The BAI has demonstrated high reliability and validity in a variety of studies both clinical samples (coefficient alpha=0.82) and non-clinical samples (coefficient alpha=0.91) (Beck et al., 1998; Borden, Peterson & Jackson, 1991).

4.6.1.3 The Discomfort Intolerance Scale

The Discomfort Intolerance Scale (DIS) is a 5-item self-report questionnaire which measures the degree to which individuals are able to tolerate physical discomfort including pain and bodily sensations. Items include “I have a high pain threshold” and “I can tolerate a great deal of physical discomfort”. Participants responded using a 7-item Likert Scale ranging from 0 (Not at all like me) to 6 (Extremely like me). The DIS has demonstrated sound reliability and validity (Schmidt, Richey and Fitzpatrick, 2006).

4.6.1.4 The State-Trait Anxiety Inventory

The State/Trait Anxiety Inventory (STAI) is a self-report questionnaire comprised of two 40-item scales designed to assess the intensity of feelings of anxiety and distinguishes between state anxiety (a temporary condition experienced in specific situations) and trait anxiety (a general tendency to perceive situations as threatening) (Speilberger, Gorsuch and Lushene, 1970). The State Anxiety Scale consists of 20 statements that evaluate how respondents feel “right now, at this
moment”, for example, “I feel at ease”. Respondents self-rate on a 4 point scale: “not at all”, “somewhat”, “moderately so”, and “very much so”. The Trait Anxiety Scale consists of 20 statements that evaluate how respondents feel “generally”, i.e. “I am a steady person”. Respondents indicate their responses on a 4 point scale: “almost never”, “sometimes”, “often”, and “almost always”. Both state and trait anxiety scales have adequate psychometric properties (Knight, Waal-Manning & Spears, 1983).

4.6.1.5 The Panic Attack Cognitions Questionnaire

The Panic Attack Cognitions Questionnaire (PACQ) assesses the degree of preoccupation with 25 typical cognitions that occur during a panic attack. This scale was used to measure participants’ severity of panic related cognitions. Respondents are asked to rate each thought on a 4-point scale indicating their level of preoccupation with that thought, from 0 = not at all, to 3=totally dominates my thoughts. Examples of the 25 cognitions include, “I must have a brain tumor” and “I will be paralyzed with fear”. The sum of the 25 item scores provides a total PACQ score. The PACQ has demonstrated good internal consistency (Cronbach alpha .88) and has shown to be a valid measure with discriminant function analysis indicating the PACQ’s unique contribution in differentiating individuals with and without panic attacks (Clum, 1990).

4.6.1.6 The Acute Panic Inventory

The Acute Panic Inventory (API) is a 17-item self-report inventory designed to measure the severity of symptoms that typically occur during spontaneous panic attacks in patients with PD (Liebowitz et al., 1984). Each of the 17 items on the scale
represents one common symptom of a panic attack which respondents self-rate the severity on a 4 point scale; where 0 = symptom not experienced, 1.0 = slight experience, 2.0 = moderate experience, and 3.0 = severe experience of symptom. Examples of the items include, “Are you fearful?” and “Do you have rapid or difficulty breathing?” The API can be administered in minutes and yields a total score ranging between 0 – 51. Respondents can be asked to respond to the API as if they were (1) currently experiencing a panic attack, (2) currently experiencing a period of marked stress, or (3) as they feel at the moment.

4.6.1.7 The Visual Analog Scale

The Visual Analog Scale (VAS) provides a simple technique for measuring subjective experience. They have been established as valid and reliable in a range of clinical and research applications (Carlsson, 1982). The scale consists of a 10 cm horizontal line, anchored by the words “not at all anxious” on the extreme left hand side, and the words “extremely anxious” on the extreme right hand side. Participants are provided with the instructions, “Mark the line below with a vertical stroke to show the level of anxiety you are feeling at the moment. A mark at the extreme right would show that you are feeling the most anxious you could ever imagine. A mark near the centre would show that you feel moderately anxious”. A higher score indicates greater anxiety.

4.6.1.8 The Center for Epidemiological Studies Depression Scale

The Center for Epidemiological Studies Depression Scale (CES-D) measures current depressive symptomatology related to major or clinical depression in adults and adolescents. The CES-D comprises 20 items which tap into depressed mood,
feelings of guilt, worthlessness and helplessness, psychomotor retardation, loss of appetite and sleep difficulties. Internal consistency is excellent for the CES-D 20 (Cronbach’s $\alpha = .88-.91$), and test-retest reliability is excellent (ICC = 0.87) (La Chapelle, 2005, Miller et al., 2008). It has demonstrated ranges in validity from Pain (Pearson’s $r = 0.27$) to Mental Health (Pearson’s $r = 0.75$) and adequate with the Fatigue Severity Scale (Pearson’s $r = 0.58$) (Kuptniratsaikul et al, 2002, Miller et al, 2008, Anton et al., 2008).

4.6.2 Physiological Measures

As part of the experimental procedure for the first two studies, physiological data, mainly heart rate, respiration rate and oxygen saturation (SaO$_2$) levels were also monitored and collected throughout.

4.6.3 Respiratory Challenges and Cold Facial Immersion Task

4.6.3.1 Breath-hold challenge

The breath-hold challenge was undertaken by all participants who were part of the first study (Chapter 5). Participants wore a nose clip and were instructed to hold their breath for as long as possible, following an exhalation. Upon completion of this breath-hold challenge, they were given one minute rest period before being instructed again to hold their breath after taking a maximum inhalation. Breath-hold time in seconds was taken as a measure, and physiological measures including heart rate (HR) and respiration rate were recorded as part of this challenge.
4.6.3.2 Cold Facial Immersion Task

Upon provision of informed written consent, all participants took part in the experimental study which involved a cold-facial immersion (CFI) task. This experimental condition was present in both the first (Chapter 5) and the second study (Chapter 6) reported in this thesis.

A sterilised container was filled with water and placed on the left side of a medical bed which was cleared of any other apparatus. There was sufficient space around the water container to allow participants room to rest their arms on each side of the container whilst completing the task. Participants were instructed to take a maximal vital capacity inhalation and then immerse their entire face in the water (including the forehead), whilst holding their breath for thirty seconds. Participants were informed that they could terminate the exercise at any time if they felt discomfort or a strong urge to breathe. The researcher counted out aloud in intervals of 5 seconds until 30 seconds was reached, at which point participants were asked to lift their face from the water. The ambient air temperature was controlled at 22°C and the water temperature was maintained between 7-12 °C. A thermometer was used to ensure the water temperature was maintained within this range. A digital pulse oximeter was also used with participants to measure oxygen saturation (SaO₂) levels during the CFI tasks, as the researchers were interested in seeing whether the SaO₂ levels changed during the CFI task.

4.6.3.3 CO₂ Challenge

For the CO₂ challenge, participants were instructed to take in a single inhalation of a 35% CO₂ and 65% O₂ gas mixture and to hold their breath for 4
seconds before exhaling. Physiological measures including heart rate (HR) and respiration rate (RR) were recorded using a Zephyr Bioharness which involved the participant being fitted with a chest strap. Participants’ SaO₂ levels were monitored using a finger pulse oximeter. Upon completion of this task, participants were required to complete a battery of self-report measures including; the ASI, BAI, STAI (State), PACQ, API, and VAS (Participant). The researcher also completed the VAS (Researcher) scale based on their perception of the participant’s anxiety to cross-validate participant ratings.

4.6.4 Physiological Materials

4.6.4.1 Electrocardiogram (ECG)

A compact physiological monitoring system (Zephyr Bioharness), featuring a chest strap and external multi recording and monitoring device was used to measure heart rate, posture, breathing wave and respiration rate. Participants were connected to the Zephyr Bioharness and measured throughout the experimental study. Participant’s breath-hold ability was also measured during the experimental phase and included breath-hold ability after exhalation, and breath-hold ability following maximum inhalation.

4.6.4.2 Pulse Oximeter

A finger pulse oximeter was used to monitor the participants’ oxygen saturation (SaO₂) levels in the blood as well as pulse rate. The pulse oximeter was attached to the participant’s fingers throughout the CO₂ challenge and CFI exercises conducted in the study. Part way through the study the use of the pulse oximeter was discontinued,
as it was difficult for the researcher to record SaO\textsubscript{2} levels on a second to second basis and these measures were not the focus of the investigation in this study.

4.6.4.3 CO\textsubscript{2} Inhalation Materials

For the CO\textsubscript{2} challenge, a pre-mixed gas containing 35% CO\textsubscript{2} and 65% O\textsubscript{2} was administered through a Douglas Bag. The CO\textsubscript{2} challenge was administered by the principal researcher who was trained to use the equipment. A medical specialist was also available during the experimental study in case participants required medical attention or in case of emergency. Equipment was sterilised prior to each use and a one way valve was used to prevent cross contamination between participants.
Chapter 5

PRELIMINARY INVESTIGATION:
RESPIRATORY CHALLENGES AND COLD FACIAL IMMERSION

5.1 AIM

This preliminary study is the first of two studies which aim to investigate the application of the diving response (DR), cold facial immersion (CFI) and breath-holding, by examining the effects of this human adaptation on panic symptoms and cognition in clinical participants and control participants. The present study specifically aimed to investigate the immediate effects of breath-holding and cold facial immersion (CFI) on panic symptoms and cognition. The objectives of the present study were to (1) examine preliminary data on the short term effects of CFI on physiological and psychological panic symptoms; (2) compare a group of PD participants with a control in order to examine the magnitude of differences between these groups. This study is the first attempt to examine applications of the DR and CFI to treat panic symptoms.
5.2 HYPOTHESES

5.2.1 Hypothesis 1

That clinical participants will have shorter breath-hold durations than healthy controls in both breath-hold challenges in line with Klein’s suffocation alarm hypothesis.

5.2.2 Hypothesis 2

That clinical and control participants will experience a heart rate reduction in response to the cold facial immersion (CFI) tasks, as a result of the activation of the diving response (DR). Furthermore, it is hypothesised that there will be no significant difference in heart rate reduction between clinical and control participants.

5.2.3 Hypothesis 3

That clinical participants will demonstrate increased heart rate and respiration rate in response to the CO2 challenges when compared to control participants.

5.2.4 Hypothesis 4

That clinical participants will report increased anxiety-related symptoms when compared to control participants, in response to the CO2 challenge.

5.2.5 Hypothesis 5

It is hypothesised that all participants will report significantly lower anxiety in response to the CO2 challenge with Cold Facial Immersion when compared to baseline measures and the CO2 challenge alone.
5.3 METHOD

5.3.1 Participants

A total of 38 participants were recruited to participate in this study. Of these, six participants with PD were excluded from being able to participate as part of the clinical group during the initial screening stage of the study. All six participants met the criteria for a diagnosis of PD, however, three also had other co-morbidities that were exclusion criteria, and three were taking medication and on this basis excluded from the study.

In this exploratory study, we used a pragmatic approach of recruiting as many participants as possible given time and budget constraints of this PhD research study. To accurately estimate sample size we would have required variability data for the outcomes of interest which were not available. The data from this study can be used to estimate the variability in outcomes of interest and inform sample size calculations in future studies.

Hence the final clinical and control groups comprised 32 participants; 16 patients with a primary diagnosis of panic disorder (PD) with or without agoraphobia (DSM-V) (Clinical Group 1), and 16 normal controls who did not meet criteria for PD or mental illness (Control Group 2). Of these 6 were male, and 26 were female. The clinical group comprised 1 male and 15 females, and the control group comprised 5 males and 11 females. The participants in the clinical group had an average age of 36.43 years ($SD = 2.82$), whilst the participants in the control group had an average age of 29.06 years ($SD = 1.79$). Demographic and clinical data for all participants are reported in the results section of this chapter.
5.3.2 Health Screening

The final 32 participants underwent health screening assessments and were established as medically eligible to undergo the CO₂ challenge.

5.3.3 Research Design

The experiment was conducted in a clinical setting. Participants took part in four experimental challenges as outlined in Table 1. The order of the conditions was randomly allocated to each participant.

Table 1

*Experimental Conditions*

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition A</td>
<td>2 Breath-hold challenges</td>
</tr>
<tr>
<td>Condition B</td>
<td>Cold Facial Immersion (CFI) Task</td>
</tr>
<tr>
<td>Condition C</td>
<td>CO₂ Challenge</td>
</tr>
<tr>
<td>Condition D</td>
<td>CO₂ Challenge followed by CFI Task</td>
</tr>
</tbody>
</table>

5.3.4 Measures

All participants were required to complete a battery of psychological assessments before, during and after the experimental study. Descriptions of the psychological measures utilised in this study are described in Chapter 4. Table 2 provides a list of the battery of psychological measures and the various time points at which these measures were administered throughout the experimental study.
Physiological measures including heart rate, respiration rate and breath-hold times in seconds were also recorded at various points throughout the experimental study. Figure 6 displays the experimental procedure indicating when physiological and psychological measures were collected as part of this study.

Table 2

Battery of Psychological Assessments Administered Before, During and After the Experimental Study

<table>
<thead>
<tr>
<th>Psychological Measures</th>
<th>Administrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Anxiety Sensitivity Index (ASI)</td>
<td>Pre-Test, Condition C, Condition D</td>
</tr>
<tr>
<td>2. Beck Anxiety Inventory (BAI)</td>
<td>Pre-Test, Condition C, Condition D</td>
</tr>
<tr>
<td>3. Discomfort Intolerance Scale (DIS)</td>
<td>Pre-Test,</td>
</tr>
<tr>
<td>4. State/Trait Anxiety Inventory (STAI) (A-Trait)</td>
<td>Pre-Test,</td>
</tr>
<tr>
<td>5. State/Trait Anxiety Inventory (STAI) (A-State)</td>
<td>Pre-Test, Condition C, Condition D</td>
</tr>
<tr>
<td>6. Panic Attack Cognitions Questionnaire (PACQ)</td>
<td>Pre-Test, Condition C, Condition D</td>
</tr>
<tr>
<td>7. Acute Panic Inventory (API)</td>
<td>Pre-Test, Condition C, Condition D</td>
</tr>
<tr>
<td>8. Visual Analog Scale for Anxiety (VAS) – Participant &amp;</td>
<td>Condition C, Condition D (x2)</td>
</tr>
<tr>
<td>Researcher</td>
<td></td>
</tr>
<tr>
<td>9. Center for Epidemiological Studies Depression Scale (CES-D)</td>
<td>Pre-Test,</td>
</tr>
</tbody>
</table>
Figure 6. Experimental procedure for data collection for Group 1 (Clinical) and Group 2 (Control) participants.
5.3.5 Procedure

The study was held at a clinical room at Swinburne University which was specifically set up for the research. Participants were asked to refrain from caffeine-containing beverages including cola, and smoking for at least two hours prior to testing. A compact physiological monitoring system (Zephyr Bioharness), featuring a chest strap and external multi recording and monitoring device was used to measure heart rate, posture, breathing wave and respiration rate. The PowerLab 7.0 version data acquisition and analysis software was used as a multi-recording device and recorded data were sampled at a frequency of 60hz (60 samples per minute). All participants undertook all four conditions of the experimental study whilst wearing the chest strap connected to the Zephyr Bioharness which was connected via Bluetooth to a multi-recording and monitoring device (PowerLab).

5.3.6 Data Cleaning

Prior to statistical analysis, all variables were assessed for the presence of missing data and univariate outliers. For demographic data, missing values were not replaced. For all other data, the method for identifying and treating missing values and outliers preceded as follows. Firstly, variables were inspected to identify any cases of missing data. No missing data were identified in any of the psychological measures or physiological measures collected during the pre-measure phase or experimental phase. Variables with a known, finite range were inspected for the presence of erroneous data. Data errors were checked against the original written data source (self-report measures) and corrected. The distribution of each variable was visually inspected for each group to be compared (this included Group 1 (clinical) and Group 2 (control) to identify outliers that appeared to represent measurement error.
rather than true individual differences, in accordance with the recommendations of (Tabachnick and Fidell, 2007). No outliers were identified in the clinical group or control group of participants.

Prior to conducting statistical analyses, the distributions of all variables were visually inspected to determine if they were normally distributed, a requirement of parametric statistical analyses. In cases where data did not adequately meet the assumptions of normality and could not be transformed to normalise their distributions according to recommended procedures (Tabachnick & Fidell, 2007), non-parametric analyses were conducted.

5.3.7 Statistical Analyses

Physiological data, including respiration rate (RR) and heart rate (RR) data, satisfied the assumptions for parametric analysis. Hence t-tests and ANOVA analyses were used to investigate the differences between the clinical group and control on the experimental conditions. Examination of normal distribution revealed that scores across all self-report psychological measures taken at Pre-test, after Condition C (CO₂), and after Condition D (CFI plus CO₂) including API, ASI, BAI, PACQ, STAI, VAS-R, and VAS-P were not normally distributed so non-parametric tests were utilised. Spearman’s correlation coefficient was used to investigate the relationships between psychological measures. Friedman’s test was used to examine differences in the psychological measures collected across the experimental conditions. The Statistical Package for Social Sciences version 22.0 was used for all analyses. The alpha level was set at 0.05 for all parametric analyses. A Bonferroni adjustment was
performed for parametric analyses, resulting in a significance level set at $\alpha = p < .016$.

### 5.4 RESULTS

#### 5.4.1 Overview of Analysis

The analysis of this study is presented in two sections. The first section presents the comparison of demographic details between groups and correlations of the pre-test measures. The second section presents the data analyses of study measures in relation to the hypotheses.

#### 5.4.1.1 Participant demographics and correlations between pre-measures

Age was significantly higher ($p = .035$) in the clinical group ($M = 36.4$ years; $SD = 11.3$) compared with the control group ($M = 29.1$ years; $SD = 7.2$). Tables 3 and 4 provide the means on categorical demographic variables for the clinical and control groups. No significant differences were found between the groups. Although the groups were matched statistically, there were apparent differences in gender and education that may not have been significant due to the small sample size.
# Table 3

**Demographic Information Categorical Data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (Clinical)</th>
<th>Group 2 (Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Fisher’s z</td>
<td>N</td>
</tr>
<tr>
<td>Male</td>
<td>p=.172</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Education Level</td>
<td>p=.156</td>
<td>11</td>
</tr>
<tr>
<td>No University Degree</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>University Degree</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment Status</td>
<td>p=.479</td>
<td>10</td>
</tr>
<tr>
<td>Employed</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Unemployed/Student</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>p=1.000</td>
<td>2</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinking</td>
<td>p=1.000</td>
<td>13</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Fitness</td>
<td>p=1.000</td>
<td>7</td>
</tr>
<tr>
<td>Poor/Fair</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Good/Very Good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Activity at Work</td>
<td>p=.252</td>
<td>9</td>
</tr>
<tr>
<td>Sedentary</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Non-sedentary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment status</td>
<td>p=.479</td>
<td>1</td>
</tr>
<tr>
<td>Unemployed</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Employed/Student</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly Physical Exercise</td>
<td>p=1.000</td>
<td>12</td>
</tr>
<tr>
<td>&lt; 3 hrs</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>&gt; 3 hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly Cycling</td>
<td>p=1.000</td>
<td>12</td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Some</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly Walking</td>
<td>p=.242</td>
<td>8</td>
</tr>
<tr>
<td>&lt; 3 hrs</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>&gt; 3 hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly home duties</td>
<td>p=.273</td>
<td>4</td>
</tr>
<tr>
<td>&lt; 3 hr</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>&gt; 3 hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly gardening</td>
<td>p=1.000</td>
<td>11</td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Some</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking Pace</td>
<td>p=1.000</td>
<td>4</td>
</tr>
<tr>
<td>Slow/Steady, average</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Brisk pace/Fast&gt;6km</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note.* N = 32 (group 1: n = 16, group 2: n = 16). Fisher’s exact test (2-sided).
Table 4

**Demographic Information Continuous Data**

<table>
<thead>
<tr>
<th></th>
<th>Panic</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Water Comfort (Mann-Whitney, p=.809)</td>
<td>7.31</td>
<td>2.68</td>
</tr>
<tr>
<td>(0 = Not at all comfortable - 10 = Very comfortable)</td>
<td>Average No. of Glasses per week</td>
<td>3.00</td>
</tr>
<tr>
<td></td>
<td>9.40</td>
<td>8.32</td>
</tr>
<tr>
<td>Height (Mann-Whitney, p=.468)</td>
<td>167.25</td>
<td>7.46</td>
</tr>
<tr>
<td>Weight (Mann-Whitney, p=.564)</td>
<td>74.22</td>
<td>17.97</td>
</tr>
</tbody>
</table>

*Note. p-values are based on Mann-Whitney test (2 sided).*

The Spearman rank-order correlation coefficient was used as a nonparametric measure to determine the strength and direction of association that exists between the pre-measure assessments. Table 5 provides correlations between pre-measures.
Table 5

Correlations between Pre-measure Assessments

<table>
<thead>
<tr>
<th></th>
<th>API</th>
<th>CESD</th>
<th>DIS</th>
<th>BAI</th>
<th>ASI</th>
<th>STAI T</th>
<th>STAI S</th>
<th>PACQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>-</td>
<td>.64**</td>
<td>.27</td>
<td>.69</td>
<td>.60</td>
<td>.61</td>
<td>.60</td>
<td>.60</td>
</tr>
<tr>
<td>CESD</td>
<td>-</td>
<td>.18</td>
<td>.71**</td>
<td>.84**</td>
<td>.93**</td>
<td>.83**</td>
<td>.74**</td>
<td></td>
</tr>
<tr>
<td>DIS</td>
<td>-</td>
<td>.41</td>
<td>.46</td>
<td>.13</td>
<td>.12</td>
<td>.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAI</td>
<td>-</td>
<td>.84**</td>
<td>.77**</td>
<td>.62</td>
<td>.82**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASI</td>
<td>-</td>
<td>.70</td>
<td>.62</td>
<td></td>
<td>.82**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAI Trait</td>
<td>-</td>
<td>.82**</td>
<td>.75**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAI State</td>
<td>-</td>
<td></td>
<td></td>
<td>.64</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Note. N = 30. ** p < .001

A series of t-tests for independent groups was employed to determine if significant differences existed between the clinical and the control group on the scores of all psychological measures at Time 1. The results of the analysis indicated that there were significant differences (p < .05) across all psychological measures at pre-test (Time 1), between the groups, except for the DIS (p > .05). The DIS is a measure of discomfort intolerance rather than anxiety.
5.4.2 Data Analyses

5.4.2.1 Differences between groups in Breath-hold durations (Condition A)

Two independent samples t-tests were conducted to compare the differences in breath-hold durations between the clinical and control groups. See Table 6 for descriptive statistics and t-test results for the breath-hold tasks for both groups.

Table 6

Results of t-test and Descriptive Statistics for breath-hold (BH) tasks for Clinical and Control groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Clinical (n = 16)</th>
<th>Control (n = 16)</th>
<th>95% CI for Mean Difference</th>
<th>T</th>
<th>Df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BH p. max inhalation</td>
<td>44.05 18.17</td>
<td>53.30 18.03</td>
<td>-22.31, 3.82</td>
<td>-1.45</td>
<td>30</td>
<td>.912</td>
</tr>
</tbody>
</table>

Results revealed there were no significant mean differences between the clinical participants and control participants in their breath-hold times following a maximum inhalation (p > .05). Furthermore, when comparing mean differences in breath-hold times following a passive exhalation, no significant mean differences were found between clinical participants and control participants (p > .05).
5.4.2.2 Physiological Differences in response to Cold Facial Immersion Task  
(Condition B)

Figure 7 shows the mean average HR measured just prior to the CFI task, and  
the mean average HR measured upon completion of the CFI task. Simple main  
effects analysis showed that prior to the CFI task and upon completion of the CFI  
task, participants experienced a significant decrease in heart rate, \((F = (1, 30) = 58.87,\  
p = .00, \eta^2=.662)\). However there was no significant main effect of group, with clinical  
and control participants experiencing similar reductions in heart rate as a result of the  
CFI task \((F(1, 30) = .127, p = .724, \eta^2=.007)\).

![Figure 7. Mean Heart rate for clinical group (n = 16) and control group (n= 16) before and after cold facial immersion (CFI).](image)
5.4.2.3 Physiological Differences in response to the CO₂ Challenge (Condition C)

Table 7 shows the Mean RR measured 30 seconds before the CO₂ Challenge (Time 1) and Mean RR measured 30 seconds after CO₂ Challenge (Time 2). There was no significant interaction between the effects of group and CO₂ challenge task on participants’ RR, \( F = (1, 30) = .057, p = .814, \eta^2 = .002 \). Simple main effects analysis showed that between 30 seconds prior to the CO₂ challenge (Time 1) and 30 seconds following the CO₂ challenge (Time 2), participants experienced no significant increase in respiration rate, \( F = (1, 30) = .079, p = .780, \eta^2 = .003 \). No significant differences between respiration rates were observed between the clinical and control groups, \( F(1, 30) = 1.062, p = .311, \eta^2 = .034 \).

Table 7

*Descriptive Statistics for Time 1 and Time 2 of the CO₂ Challenge*

<table>
<thead>
<tr>
<th>Group</th>
<th>Clinical (n = 16)</th>
<th>Control (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( M )</td>
<td>( SD )</td>
</tr>
<tr>
<td>RR Time 1</td>
<td>14.09</td>
<td>3.52</td>
</tr>
<tr>
<td>RR Time 2</td>
<td>14.48</td>
<td>4.16</td>
</tr>
<tr>
<td>HR Time 1</td>
<td>92.33</td>
<td>15.13</td>
</tr>
<tr>
<td>HR Time 2</td>
<td>90.91</td>
<td>14.76</td>
</tr>
</tbody>
</table>

Furthermore, there was no significant interaction found between the effects of group and CO₂ on participants’ HR, \( F = (1, 30) = .805, p = .377, \eta^2 = .026 \). Simple main effects analysis showed that between 30 seconds prior to the CO₂ challenge (Time 1) and 30 seconds following the CO₂ challenge (Time 2), participants experienced no significant change in heart rate, \( F = (1, 30) = .497, p = .486, \eta^2 = .016 \).
In addition, no significant differences between heart rates were observed between the clinical and control group, \((F(1, 30) = .130, \ p = .721, \ η^2=.004)\).

### 5.4.2.4 Physiological response pre and post CO₂ administered prior to CFI (Condition D)

Table 8 shows the mean heart rates and respiration rates for participants before and after the CO₂ Challenge. A mixed ANOVA was conducted to compare the clinical and control group in terms of the effect of the CO₂ challenge task and group on participants’ RR and HR.

There was no significant interaction between the effects of group and CO₂ challenge task on participants’ RR, \((F = (1, 30) = .002, \ p = .966, \ η^2=.000)\). Simple main effects analysis showed that between 30 seconds prior to the CO₂ challenge (Time 1) and 30 seconds following the CO₂ challenge (Time 2), participants experienced no significant increase in respiration rate, \((F = (1, 30) = 4.381, \ p = .045, \ η^2=.127)\). No significant differences between respiration rates were observed between the panic and normal group, \((F(1, 30) = .011, \ p = 9.19, \ η^2=.000)\).

There was no significant interaction was found between the effects of group and CO₂ on participants’ HR, \((F = (1, 30) = .074, \ p = .788, \ η^2=.002)\). Simple main effects analysis showed that between 30 seconds prior to the CO₂ challenge (Time 1) and 30 seconds following the CO₂ challenge (Time 2), participants experienced no significant change in heart rate, \((F = (1, 30) = 1.861, \ p = .183, \ η^2=.058)\). In addition, no significant differences between heart rates were observed between the clinical and control group, \((F(1, 30) = .001, \ p = .970, \ η^2=.000)\).
Table 8

Descriptive Statistics for Heart Rate and Respiration rate before and after CO₂ Challenge

<table>
<thead>
<tr>
<th>Group</th>
<th>Clinical (n = 16)</th>
<th>Control (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>RR b CO₂</td>
<td>15.80</td>
<td>3.60</td>
</tr>
<tr>
<td>RR p CO₂</td>
<td>14.74</td>
<td>3.61</td>
</tr>
<tr>
<td>HR b CO</td>
<td>88.95</td>
<td>15.22</td>
</tr>
<tr>
<td>HR p CO₂</td>
<td>91.16</td>
<td>15.11</td>
</tr>
</tbody>
</table>

5.4.2.5 Physiological response pre and post the CO₂ + CFI task (Condition D)

Figure 8 shows the Mean HR at the start of the CFI following the CO₂ challenge and the Mean HR at the completion of the CFI task. A mixed ANOVA was conducted with the clinical and control group to examine the effect of CFI following the CO₂ Challenge on participants’ HR and examine whether differences between groups were observed. There was no significant interaction between the effects of group and CFI on participant’s HR, ($F(1, 30) = .222, p = .641, \eta^2=.007$). Simple main effects analysis showed that between Time 1 (start of CFI task following CO₂ challenge) and Time 2 (end of CFI task), participants experienced a significant HR reduction, ($F(1, 30) = 58.878, p <.01, \eta^2=.662$). This was a very large effect size. However no significant differences between the clinical and control group were observed, ($F(1, 30) = .127, p = .724, \eta^2=.004$).
Figure 8. Heart rate for clinical group (n = 16) and control group (n = 16) at the start and completion of the cold facial immersion task following CO₂ Challenge.

5.4.2.6 Psychological Measures and the effects of CO₂ and CFI

Mann Whitney U test was used to examine differences in the psychological measures collected across the three time periods. The PD group has significantly higher scores compared to the control group on all psychological measures at Time 1 (Pre-test), Time 2 (CO₂), and Time 3 (CFI after CO₂) (p<0.05), with the exception of the Discomfort Intolerance Scale (DIS) (p = .09). Table 9 provides means for all self-report psychological measures taken at Time 1 (Pre-test), Time 2 (CO₂), and Time 3 (CFI after CO₂).
Table 9

*Medians, Minimum, Maximum and Interquartile Ranges for Psychological Measures at Time 1, Time 2 and Time 3.*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mdn</th>
<th>Min</th>
<th>Max</th>
<th>Interquartile Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Panic Inventory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1 (Pre-test)</td>
<td>2.5</td>
<td>0</td>
<td>28</td>
<td>6</td>
</tr>
<tr>
<td>Time 2 (CO₂ challenge)</td>
<td>11.5</td>
<td>0</td>
<td>45</td>
<td>17.25</td>
</tr>
<tr>
<td>Time 3 (CO₂ with CFI)</td>
<td>1</td>
<td>0</td>
<td>39</td>
<td>6.5</td>
</tr>
<tr>
<td><strong>Anxiety Sensitive Index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1 (Pre-test)</td>
<td>21.5</td>
<td>0</td>
<td>59</td>
<td>19</td>
</tr>
<tr>
<td>Time 2 (CO₂ challenge)</td>
<td>21.5</td>
<td>3</td>
<td>63</td>
<td>23</td>
</tr>
<tr>
<td>Time 3 (CO₂ with CFI)</td>
<td>10</td>
<td>0</td>
<td>63</td>
<td>22.5</td>
</tr>
<tr>
<td><strong>Beck Anxiety Inventory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1 (Pre-test)</td>
<td>11</td>
<td>0</td>
<td>47</td>
<td>28.1</td>
</tr>
<tr>
<td>Time 2 (CO₂ challenge)</td>
<td>17</td>
<td>2</td>
<td>60</td>
<td>27.25</td>
</tr>
<tr>
<td>Time 3 (CO₂ with CFI)</td>
<td>3</td>
<td>0</td>
<td>62</td>
<td>9</td>
</tr>
<tr>
<td><strong>Panic Cognitions Questionnaire</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1 (Pre-test)</td>
<td>17</td>
<td>0</td>
<td>45</td>
<td>27.75</td>
</tr>
<tr>
<td>Time 2 (CO₂ challenge)</td>
<td>7</td>
<td>0</td>
<td>68</td>
<td>18.25</td>
</tr>
<tr>
<td>Time 3 (CO₂ with CFI)</td>
<td>0</td>
<td>0</td>
<td>69</td>
<td>5.5</td>
</tr>
<tr>
<td><strong>State Anxiety Inventory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1 (Pre-test)</td>
<td>38</td>
<td>21</td>
<td>71</td>
<td>17.5</td>
</tr>
<tr>
<td>Time 2 (CO₂ challenge)</td>
<td>44.5</td>
<td>24</td>
<td>79</td>
<td>22</td>
</tr>
<tr>
<td>Time 3 (CO₂ with CFI)</td>
<td>32</td>
<td>9</td>
<td>66</td>
<td>14.5</td>
</tr>
<tr>
<td><strong>VAS – Participant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1 (Pre-test)</td>
<td>7</td>
<td>0</td>
<td>9</td>
<td>5.38</td>
</tr>
<tr>
<td>Time 2 (CO₂ challenge)</td>
<td>6</td>
<td>0</td>
<td>10</td>
<td>6.13</td>
</tr>
<tr>
<td>Time 3 (CO₂ with CFI)</td>
<td>2</td>
<td>0</td>
<td>8</td>
<td>3.13</td>
</tr>
<tr>
<td><strong>VAS – Researcher</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Time 1 (Pre-test)</td>
<td>7.25</td>
<td>0</td>
<td>10</td>
<td>4.75</td>
</tr>
<tr>
<td>Time 2 (CO₂ challenge)</td>
<td>7</td>
<td>1</td>
<td>10</td>
<td>6.25</td>
</tr>
<tr>
<td>Time 3 (CO₂ with CFI)</td>
<td>2</td>
<td>0</td>
<td>7.5</td>
<td>2.75</td>
</tr>
</tbody>
</table>

*Note.* N = 32 (group 1: n =16, group 2: n = 16).
Specifically, Friedman’s test was used to examine differences in the psychological measures collected across the three time periods. API ratings were significantly different across the three times, $\chi^2(2) = 29.540, p < .01$. Post-hoc analysis with Wilcoxon signed-rank test was conducted with a Bonferroni correction applied, resulting in a significance level set at Alpha = $p < .016$. The median API ratings were 2.5 at Time 1, 11.5 at Time 2, and 1.0 at Time 3. A significant increase was seen between Time 1 and Time 2, $Z = -3.393, p > .001 .016$ and a significant decrease was observed between Time 2 and Time 3, $Z = -4.407, p < .001$. Figure 9 displays a box plot of participants’ API scores measured at baseline (Time 1), following the CO2 challenge (Time 2), and after CO2 challenge followed by CFI task (Time 3).

![Box plot of API scores](image)

**Figure 9. Median and interquartile range of API scores for all participants (clinical group and control group (N= 32) at Time 1*, Time 2*, Time 3* (* p < .05)**
ASI ratings were significantly different across two times, \( \chi^2(2) = 22.252, p < 0.01 \). Post hoc analysis with Wilcoxon signed-rank tests was conducted with a Bonferroni correction applied, resulting in a significance level set at Alpha = \( p < 0.016 \). The median ASI ratings were 21.5 at Time 1, 21.5 at Time 2, and 10.0 at Time 3. There were no significant differences between the participants’ baseline ASI measures and those taken at time 2, following the CO\(_2\) challenge, \( Z = -0.160, p = 0.016 \). A statistically significant decrease was seen between Time 1 and Time 3, \( Z = 3.911, p < 0.001 \) and between Time 2 and Time 3, \( Z = 4.097, p < 0.001 \). Figure 10 displays a box plot of participants’ API scores measured at baseline (Time 1), following the CO\(_2\) challenge (Time 2), and after CO\(_2\) challenge followed by CFI task (Time 3).

**Figure 10.** Median and interquartile range for ASI scores for all participants (clinical and control groups) (\( N = 32 \)) at Time 1*, Time 2*, Time 3* (* \( p < 0.05 \)).
BAI ratings were significantly different across the three times, $\chi^2(2) = 19.820$, $p < 0.01$. Post-hoc analysis with Wilcoxon signed-rank test was conducted with a Bonferroni correction applied, resulting in a significance level set at Alpha $= p < .016$. The median BAI ratings were 11 at Time 1, 7 at Time 2, and 3 at Time 3. A significant decrease was seen between baseline and Time 3, $Z = 3.183$, $p = .001$. A significant decrease was observed between Time 2 and Time 3, $Z = 4.436$, $p < .001$. Figure 11 displays a box plot of participants’ BAI scores measured at baseline (Time 1), following the CO₂ challenge (Time 2), and after CO₂ challenge followed by CFI task (Time 3).

![Box plot of BAI scores](image)

**Figure 11.** Median and interquartile range BAI scores for all participants (clinical group and control group (N= 32) at Time 1*, Time 2*, Time 3* (* p < .05).
PACQ ratings were found to be significantly different across the three times, \( \chi^2(2) = 18.589, p < 0.01 \). Post-hoc analysis with Wilcoxon signed-rank test was conducted with a Bonferroni correction applied, resulting in a significance level set at Alpha = \( p < .016 \). The median PACQ ratings were 17 at Time 1, 7 at Time 2, and 1 at Time 3. A significant decrease was seen between baseline and Time 3, \( Z = 2.950, p = .003 \). A significant decrease was observed between time 2 and Time 3, \( Z = 4.069 p < .01 \). Figure 12 displays a box plot of participants’ PACQ scores measured at baseline (Time 1), following the CO\(_2\) challenge (Time 2), and after CO\(_2\) challenge followed by CFI task (Time 3).

*Figure 12. Median and interquartile range for PACQ scores for all participants (clinical and control (N= 32) at Time 1*, Time 2*, Time 3* (*\( p < .05 \)).*
STAI ratings were significantly different across the three times, $\chi^2(2) = 17.758$, $p < 0.01$. Post-hoc analysis with Wilcoxon signed-rank test was conducted with a Bonferroni correction applied, resulting in a significance level set at $\text{Alpha} = p < .016$. The median STAI ratings were 38 at Time 1, 44.5 at Time 2, and 32 at Time 3. A significant increase was seen between Time 1 and Time 2, $Z = 2.334$, $p = .020$, whilst a significant decrease was noted between Time 1 and Time 3, $Z = 2.402$, $p = .016$. A significant decrease was also observed between Time 2 and Time 3, $Z = 3.951$, $p < .001$. Figure 13 displays a box plot of participants’ STAI (State) scores measured at baseline (Time 1), following the CO₂ challenge (Time 2), and after CO₂ challenge followed by CFI task (Time 3).

Figure 13. Median and interquartile range for STAI (State) scores for all participants (clinical group and control group (N= 32) at Time 1*, Time 2*, Time 3* (* $p < .05$).
VAS participant were significantly different across the three times, $\chi^2(2) = 36.051, p < 0.01$. Post-hoc analysis with Wilcoxon signed-rank test was conducted with a Bonferroni correction applied, resulting in a significance level set at $\alpha = p < 0.016$. The median VAS-P ratings were 7 at Time 1, 6 at Time 2, and 2 at Time 3. A significant decrease was seen between Time 1 and Time 3, $Z = 4.691, p = 0.001$, and between Time 2 and Time 3, $Z = 4.767 p < 0.001$.

Figure 14 displays a box plot of VAS-Participant scores measured at baseline (Time 1), following the CO$_2$ challenge (Time 2), and after CO$_2$ challenge followed by CFI task (Time 3).

![Figure 14. Median and interquartile range for VAS-Participant scores for all participants (clinical group and control group ($N = 32$) at Time 1*, Time 2*, Time 3* (*$p < .05$).]
VAS Researcher ratings were also significantly different across the three times, $\chi^2(2) = 36.051, p < 0.01$. Post-hoc analysis with Wilcoxon signed-rank test was conducted with a Bonferroni correction applied, resulting in a significance level set at $\text{Alpha} = p < 0.016$. The median VAS-R ratings were 7.25 at Time 1, 7 at Time 2, and 2 at Time 3. A significant decrease was seen between Time 1 and Time 3, $Z = 4.507, p = 0.001$, and between Time 2 and Time 3, $Z = 4.767, p < 0.001$. Figure 15 displays a box plot of participants’ VAS Researcher scores measured at baseline (Time 1), following the CO$_2$ challenge (Time 2), and after CO$_2$ challenge followed by CFI task (Time 3).

![Box plot of VAS Researcher scores](image)

**Figure 15. Median and interquartile range for VAS-Researcher scores for all participants (clinical group and control group (N= 32) at Time 1*, Time 2*, Time 3* (* $p < .05$).**
5.5 DISCUSSION

The principal findings of the current investigation indicate that there were no significant differences in breath-hold durations amongst the clinical and control participants. Overall, the CO₂ challenge evoked anxiety and panic symptoms as self-reported by clinical participants and the cold facial immersion (CFI) task demonstrated anxiolytic effects by reducing heart rate, as well as self-reported symptoms of anxiety and panic in both the clinical and control group. The findings of this preliminary study are discussed in light of each relevant hypothesis.

Hypothesis 1: There was no significant difference in breath-hold (BH) ability between the clinical and control group. Whilst the means of the BH durations in both the passive exhalation and the maximum deep inhalation BH tasks were slightly lower for the clinical group as compared to the control group, these differences were not significant. One possible explanation for this finding may have been the relatively small sample size that comprised this study. Hence the findings of this study did not support this hypothesis. Previous research which has tested this hypothesis have used different methodologies and yielded varied findings (van der Does, 1997; Asmundson & Stein, 1994; Roth et al., 1998; Zandbergen et al, 1992, Nardi et al, 2002). The varied results found in previous studies may be explained by many of the studies comprising small, heterogeneous samples, diverse inclusion and exclusion criteria, and different criteria for assessing panic attacks (PA).

Furthermore, these findings do not provide support for Klein’s theory, which suggests that the brain’s suffocation detector incorrectly signals a lack of useful air and increases vulnerability to false suffocation alarms and PAs. Furthermore, these
findings do not support the breath-hold challenge as a potential marker for CO₂ hypersensitivity to CO₂ induced panic. Hypersensitivity to CO₂ may be more notable in the PD respiratory subtype as suggested by (Biber & Alkin, 1999; Gorman et al., 1994; Papp et al., 1995; Perna et al., 1995; Nardi et al., 2004, 2006; Sardinha et al., 2009). The small sample in this study and our recruitment method (general rather than selecting sub-groups) precluded subgroup analysis. According to Nardi et al. (2002), respiratory symptoms may play a role in both PAs and CO₂ induced panic. Their study reported that with a single breath of 35% CO₂/65% O₂ inhalation participants with PD reported significantly stronger symptoms of panic and anxiety than the control group. These findings were in line with those of Griez et al. (1987) and Perna et al. (1994).

Hypothesis 2: In this study, it was expected that clinical and control participants will experience a reduced heart rate (HR) in response to the CFI task. This is in line with previous research that has demonstrated that the diving response (DR) elicits a strong autonomic response characterised by a pronounced HR reduction and blood centralisation to the organs that are most in need of oxygen (i.e., heart, lungs and brain) (Asmussen & Kristiansson, 1968; Ferringo et al., 1997; Foster & Sheel, 2005; Hong & Rahn, 1967; Schagatay & Andersson, 1998; Schagatay et al., 2000). The results of the current study support this hypothesis and found that both clinical and control participants demonstrated a significant bradycardiac effect (a drop of approximately 30-35 beats per minute) following the CFI task. Hiebert and Burch (2003), and Reyners et al. (2000) in their studies reported an average HR reduction of approximately 20 beats per minute. Most studies have demonstrated HR reductions between 25%- 40% following cold facial immersion (Andersson et al., 2002, 2004;
Lindholm et al., 1999, 2002) demonstrated a HR decrease between 33% and 35%. In the current study, cold facial immersion bradycardia reached a peak within 20 to 30 seconds, which is consistent with previous research (Andersson & Schagatay, 1998; Baranova et al., 2017; Sterba & Lundgren 1988; Gooden, 1994; Ferrigno et al., 1986; Lindholm & Lundgren, 2009). No differences between groups were observed as both groups had a comparable HR reduction, in response to the CFI task, regardless of how they responded to the CO₂ challenge. The findings of the current study suggest that the DR is a powerful physiological adaptation that is innate to all humans. This is in line with previous research that has found that the DR is augmented by the CFI task or by facial cooling (Yadav et al., 2017; Khurana & Wu, 2006, Schagatay, 2009).

Hypothesis 3: It was hypothesised that clinical participants would demonstrate higher CO₂ sensitivity in response to the CO₂ challenge as evidenced by increased HR and RR when compared to control participants. No significant differences were found between the clinical and control groups in heart rate in response to CO₂. Previous research has yielded mixed results with some CO₂ studies reporting an increase in HR (La Pierre et al., 1984, Liebowitz, et. al., 1985; Woods, et al., 1988; Charney et al., 1987a; Poonai et al., 2000; Schmidt, Richey, Maner et al., 2006) and some reporting a decrease or no change in HR (Nicolai et al., 2008; Gorman et al., 1990).

Furthermore, this study reported no significant difference in respiration rates between the clinical and control group. Although previous research examining respiration rate (RR) post CO₂ has yielded mixed results, our findings lend support to those of Griez and van det Hout (1983; 1986), Klein (1993), and Schimitel et al. (2012) which reported no significant differences in respiration rates following CO₂.
inhalation. Contrary, to the findings of van den Hout and Griez, (1984), the CO₂ challenge did not induce a significant increase in RR in clinical and control participants. Previous studies have reported that 50% of clinical panic participants describe difficulties with taking a deep inhalation of CO₂ and feeling breathlessness (Perna et al., 2004b). This difficulty was also observed with the clinical group in this study, with some participants reporting discomfort in breathing and with the bad odour. Hence it is plausible that the full effects of CO₂ were not observed as some participants may not have taken a full inhalation of CO₂. According to Griez and van den Hout (1986) in order for the 35% CO₂ test to be valid, a participant needs to inhale at least 80% of their vital capacity.

Hypothesis 4: It was hypothesised that clinical participants would report increased anxiety symptoms when compared to control participants, in response to the CO₂ challenge. The results of this study indicate that, compared to the controls, the clinical participants reported experiencing more anxiety and panic symptoms including panic cognitions and anxiety sensitivity in response to the CO₂ challenge on the following anxiety measures; Anxiety Sensitivity Index (ASI), Acute Panic Inventory (API), State and Trait Anxiety Inventory (STAI), Panic Attack Cognitions Questionnaire (PACQ), Beck Anxiety Inventory (BAI), Visual Analogue Scale completed by the participant (VAS-P) and researcher (VAS-R). This finding is in line with previous research which has reported increased anxiety symptoms as measured by self-reports on anxiety measures and researcher observations following the CO₂ challenge (Beck, Ohtake & Shiperd, 1999; Battaglia et al., 1995). In some studies, healthy controls have reported a rise in anxiety symptoms, following the 35% CO₂ challenge (Gorman et al., 2001; Griez & van den Hout, 1986; Harrison et al., 1989;
Woods et al., 1988), however this is not comparable to PD participants who display heightened anxiety and panic symptoms (Griez & Verburg, 1998; Papp et al., 1993; Verburg et al., 1995). In a placebo controlled experiment the 35% CO₂ challenge provoked the interoceptions characteristic of panic attacks in healthy controls which were observed to largely overlap with those reported by clinical participants (Griez, & van den Hout, 1982; Harrison et al., 1989; van den Hout & Griez, 1984). Harrison et al. (1989) in their study reported increases in the Acute Panic Inventory (API) and anxiety ratings following the CO₂ challenge in control participants. However despite control participants experiencing anxiety, very rarely do they experience PAs in response to the CO₂ challenge (Perna et al., 1995).

The findings of the current study indicate that clinical participants reported increased anxiety compared to control participants however this hypothesis was not able to be completely tested due to limitations in the data. As the self-report measures were not normally distributed, non-parametric statistics were used to examine the effects of pre and post CO₂ using repeated measures (Friedman’s and Wilcoxon signed-rank tests). However, these statistics did not allow for a comparison of the pre and post effects, and more specifically the increase in heart rate between groups for the study conditions.

Furthermore, it appears that both groups may have experienced some anticipatory anxiety with the clinical group, reporting elevated levels of anxiety at Time 1. In relation to the CO₂ challenge, the clinical group had more elevated anxiety as measured by the anxiety measures administered at Time 2, as compared to the control group. In the control group, although the ASI and the STAI scale scores were
much lower than the clinical group, they were somewhat elevated as compared to all the other anxiety measures at Time 1. A possible explanation could be that control participants may have experienced some anticipatory anxiety with respect to the experimental design.

Hypothesis 5: It was hypothesised that all participants will report significantly lower anxiety in response to the CO₂ challenge with Cold Facial Immersion (CFI) when compared to baseline measures and the CO₂ challenge alone. The findings of this study support this hypothesis. All anxiety measures including the ASI, API, STAI, PACQ, BAI, VAS-P, and VAS-R were lower at Time 3 (CO₂ with CFI) compared to Time 1 (baseline) with the exception of API. This makes sense as control participants scored lower on the API, as they did not experience a PA in response to the CO₂ challenge. Furthermore, all participants reported a significant decrease in anxiety symptoms across all of the measures between Time 2 (CO₂ Challenge) and Time 3 (CO₂ with CFI). The findings of this study lend support to the application of the diving response and CFI in reducing panic cognitions and symptoms of anxiety and panic. Furthermore, these results indicate some promise in terms of the utility of CFI in assisting with the management and reduction of anxiety and panic symptoms.

In view of the small sample size, the results of this study need to be interpreted with caution. With regard to breath-hold (BH) durations, our findings were not in line with the findings of Asmundson and Stein (1994) who found that patients diagnosed with PD had significantly shorter BH durations than healthy participants. Our findings were not in line with Klein’s (1993) theory of the suffocation false alarm
theory, and the findings of Asmundson and Stein (1994), who suggested that participants with PD terminate their BH earlier in order to avoid activation of the suffocation alarm. A plausible explanation for why we did not yield the results we expected may have been due to the relatively small sample size of the clinical group. Future research of breath-hold durations between clinical and control groups should look at investigation with a larger sample size that is adequately powered.

The current findings are consistent with Harrison et al. (1988), who found no significant differences in HR changes between panic patients and controls following the CO₂ challenge, even though there was a trend for the heart rate increasing. It is well established in the literature that CO₂ induced hyperventilation, elicits a sudden increase in ventilation accompanied with a surge of anxiety that mimics a PA (Klein, 1993; Griez & van der Hout, 1986) and triggers arousal of the conditioned fear response in panic patients (Sinha et al., 2000; MacKinnon, Craighead & Hoehn-Saric, 2007). Woods, Charney, Goodman and Heninger (1988) in their study demonstrated that the panic patients who experienced CO₂-induced panic attacks (PAs) showed HR responses to CO₂ that were significantly greater than those of the non-panicking patients, perhaps reflecting greater cardiac sympathetic stimulation by CO₂.

Moreover, in response to the CO₂ challenge, reports from the literature indicate that patients tend to experience remarkable hyperventilation and subsequent cognitive symptoms of anxiety (Klein, 1993). Both healthy and people diagnosed with an anxiety disorder report feeling anxiety symptoms following CO₂ inhalation (Woods et al., 1986; Gorman et al., 1984; van der Hout & Griez, 1984). However, the response in normal controls, as well as individuals suffering from generalised anxiety
disorder (GAD), is generally much weaker than individuals suffering from PD (Griez, Zandbergen, Pols & de Loof, 1990). Both healthy and anxious patients produce anxiety following CO₂ inhalation (Woods et al., 1986; Gorman et al., 1984; van det Hout & Griez, 1984). However it is unlikely that CO₂ evokes all 13 possible symptoms of PD, and there is reported variability in the intensity of the symptoms experienced (Perna et al., 1994). Individual sensitivity to the CO₂ challenge and to increased concentrations of CO₂ may have accounted for some of the challenges with the provocation study. Five out of ten studies reported greater increases in heart rate (HR), of drug-induced panic, all of which involved the administration of sodium lactate (La Pierre et al., 1984; Liebowitz, et al., 1985; Woods et al., 1988; Charney et al., 1987a).

Hence the CO₂ challenge may not be the best provocation method to induce changes in HR. Notably, Kaye et al., (2004) found a significant decrease in HR lasting 90 seconds post the CO₂ challenge. This was in line with the findings of Griez and van den Hout, (1983). On the contrary significant increases in HR post CO₂ have been noted (Poonai et al., 2000; Schmidt, Richey, Maner et al., 2006). The increase in HR perhaps reflects greater sympathetic stimulation and noradrenergic neuronal function (Woods et al., 1988). Research comparing PD with controls on their HR response is limited, and two studies yielded no significant differences in neither of the groups, in HR change from baseline to post CO₂ inhalation (Nicolai et al., 2008; Gorman et al., 1990).

A key finding of the study was that there was a significant increase in anxiety symptomatology between Time 1 (baseline) and Time 2 (following CO₂ challenge) on
the following measures Acute Panic Inventory (API) and State Anxiety (STAI) as reported by PD participants. This suggests that a number of clinical participants may have experienced a panic attack or elevated anxiety levels induced by the CO₂ inhalation. On the contrary, a number of participants may have had reduced panic symptoms at Time 2, following the CO₂ challenge, this was noted with the PACQ measure. A plausible explanation for this may be that clinical participants at Time 1, may have experienced more significant anticipatory anxiety in relation to the experimental design as compared to Time 2.

In response to the CFI task, participants had significantly reduced self-reported anxiety, as measured by the API, BAI, PACQ, STAI, at Time 3 (CO₂ with CFI) when compared to Time 1 (baseline). Also, there was a significant decrease in both the VAS-P and VAS-R from Time 2 (CO₂ Challenge) to Time 3 (CO₂ with CFI). This suggests that clinical participants following the CFI task reported minimal panic or anxiety symptoms. The clinical group had significantly lower anxiety on all anxiety measures (API, ASI, BAI, PACQ, STAI) following Time 3 (CO₂ with CFI), as compared to Time 2 (CO₂ challenge). This is likely to be due to the activation of the diving response (DR), a powerful autonomic reflex which initiates a bradycardiac response.

These particular findings of this preliminary study may provide us with some novel insights. It is of particular merit to note, that by activating the DR and subsequently reducing one’s heart rate, one may observe reductions in both physiological, and cognitive symptoms of panic and potentially in CO₂ sensitivity. One of the scariest symptoms, reported by sufferers of PD is the heart racing or
pounding. Hence reducing the heart rate and the autonomic sympathetic nervous system arousal may have a positive impact on self-reported anxiety. Another common symptom reported by panic sufferers that are associated with fear are the feelings of suffocation and dyspnea. On the contrary, when the DR is activated, it has an oxygen conserving effect which extends the breath-hold with an aim to assist the organism to survive. Hence, cold facial immersion may prove to be an effective treatment for PD and other anxiety disorders. Furthermore, the DR can be easily activated with cold moisture (i.e., ice pack) making it an easy to administer treatment. Studies have demonstrated significant heart rate reductions, by the application of cooling packs on the face (Brown, Sanya & Hilz, 2003) which too activate the DR.

5.5.1 Study Limitations

A limitation of this preliminary study was the recruitment of clinical participants which proved difficult due to a number of constraints and challenges. Specifically, the extensive list of exclusion criteria for individuals to be eligible to participate in the study limited the sample. Many participants who were interested in participating had other comorbidities or were taking prescribed medication. In the current study, a number of participants were excluded based on their comorbidities. Recruitment challenges also made it hard to match participants as closely as we had planned. People with PD were significantly older on average than control participants and this may have influenced the physiological and psychological outcomes in this study.

Moreover, some candidates that expressed interest in participation did not participate as they communicated to the researcher that they did not want to
participate once informed of the experimental protocol due to their perceived fear that the CO₂ challenge may evoke a panic attack, and their perceived fear of losing control. Some candidates that expressed interest in participation may have not participated due to their perceived anxiety or discomfort involving the cold facial immersion (CFI) task, and the breath-holding (BH) tasks. Furthermore, the participants in the control group were mostly university students studying psychology, and hence the results may not be truly representative of the normal population.

There were also some difficulties noted with the breathing apparatus used for the CO₂ challenge and with the provocation method as mentioned previously. Although participants were instructed to take in a maximal vital capacity inhalation during the CO₂ challenge of a premixed gas comprising 35% CO₂ and 65% from the Douglas bag, some did not inhale deeply as instructed. Notably, this may have affected the results; both the physiological response to the CO₂ challenge as measured by changes in heart rate and respiration rate and the psychological response as measured by the anxiety measures. Moreover, not all participants were able to hold their breath with the inhaled gas mixture for a period of 4 seconds before exhaling it, as instructed. This was because some participants reported that they did not like the taste, and some participants found the CO₂ challenge elicited some symptoms that made them reportedly anxious or panicky. Although participants were reassured that is a completely safe procedure, and all they may experience is some transient breathlessness, one may anticipate that the CO₂ challenge may have evoked some anxiety and hence they did not comply with the instructions of the task. This was particularly observed in some PD participants who demonstrated some difficulty with the inhalation of the CO₂ challenge. The participants who were observed to have had
difficulty doing this, may not have had a marked physiological response, following the CO₂ challenge, as they may not have had the transient breathlessness or the elevated heart rate. Given that to be considered a valid test, participants need to inhale at least 80% of their vital capacity of CO₂ (Griez & van den Hout, 1986), our results may have been impacted by the inability of some participants in achieving this. Given the brevity of the task, it was not anticipated that participants would experience difficulty in carrying out the CO₂ challenge as per instructions. Future studies should emphasise the importance of a maximum inhalation and maintaining the breath-hold for 4 seconds to participants.

Another important limitation was that results were variable for each individual. For example, some participants experienced transient breathlessness immediately after the CO₂ challenge, whereas with others there was a delay. For the purposes of our statistical analysis, mean data were compared 30 seconds prior to the CO₂ challenge with 30 seconds post CO₂ challenge, hence it was difficult to capture unique differences in individual participants. However, when data were examined on a case by case basis, a trend is depicted, characterised by a more elevated respiration rate (RR) and heart rate (HR) in the clinical participants in response to the CO₂ challenge, when compared to the control group. The data proved to be difficult to interpret due to the increased variability in response to the CO₂ challenge. Some participants experienced an increase in RR immediately after the CO₂ challenge, whereas others had a delayed response up to a minute or two following the CO₂ challenge. Furthermore, there was also variability in the HR increase following the CO₂ challenge, some participants had an increase in HR immediately after the CO₂ challenge, whereas in others there was a delayed response. It was also observed that
in some cases the increase in HR and RR was not concurrent following the CO₂ challenge, but rather the increased responses in HR and RR were noted at different time intervals. This was an important limitation of the study, as comparing 30 seconds of physiological data 30 seconds prior to the CO₂ challenge to 30 seconds following the CO₂ challenge, did not provide us with an accurate reflection of the RR and HR rate fluctuations. Previous research has yielded mixed results in regards to RR and HR changes in response to the CO₂ challenge, and found that RR and HR changes are not always concurrent (La Pierre et al., 1984, Liebowitz et al., 1985; Woods et al., 1988; Charney et al., 1987a; Poonai et al., 2000; Schmidt, Richey, Maner et al., 2006; Klein, 1993 & Schmitel et al., 2012). Hence the statistical analyses conducted did not take into consideration these cardiorespiratory fluctuations post 30 seconds after the challenge, as this data was not available across all tasks.

5.6 FUTURE RESEARCH

5.6.1 Rationale for Study 2

The results of this preliminary study indicated that the cold facial immersion (CFI) had a powerful autonomic response, evidenced by a significant reduction in heart rate (HR) as well as a reduction in self-reported psychological and physiological symptoms of anxiety. Upon the completion of this study, the main findings that intrigued the researchers were that there was a marked reduction in anxiety and panic symptoms reported on anxiety measures following the CO₂ plus CFI task.

In designing Study 2, the researcher wanted to establish whether trained effects of the CFI task could change individuals’ response to the CO₂ challenge. The proposed design put forward to the Ethics committee entailed both panic and control
groups practising three daily CFI task administrations for a period of four weeks at their own home. This design posed a number of ethical and safety considerations regarding practicing the CFI task at home. Although we proposed that the CFI would be practiced under supervision in participants’ own homes, the research ethics committee were concerned that there may be public liability issues and safety, risks as participants would not have appropriate supervision at home. Hence our submitted ethics application was not approved by the Swinburne University Ethics Committee. Consequently, as a result of ethical dilemmas and time constraints, ideas exploring trained effects of the CFI were discontinued the design for the second study protocol was reviewed.

The rationale for the next study resulted primarily from the CFI having such a powerful response in terms of reducing panic and anxiety symptoms. The results warranted further exploratory investigation of CFI and more specifically the researcher thought it would be of merit to continue investigating the effects of CFI with a clinical group compared to normal controls. In reviewing the findings of the preliminary study, Condition D (CO₂ challenge, plus CFI), appeared to elicit the most notable changes in anxiety symptoms and physiological response. Hence examining this relationship further was the core focus of the next study. It was conceptualised that if Condition D is reversed and the CFI task is administered prior to the CO₂ challenge, one may be able to make inferences about the effects of CFI, on an individual’s response to the CO₂ challenge, and more specifically to CO₂ sensitivity. Based on research on the trained effects of the diving response (Konstandinidou & Chairopoulou 2017) and the findings of the preliminary study, there was value in exploring whether CFI could be used as an intervention to reduce and prevent panic
symptoms and panic attacks. Moreover, the genesis for the rationale of the second study seemed to follow a logical sequence, given that it is well established in the literature that patients with PD have higher CO₂ sensitivity (Gorman et al., 2000; Griez & Perna, 2003; Kent et al., 2001; Klein, 1993). Furthermore, the results of the preliminary study indicated that the CFI task was able to reduce both physiological symptoms and cognitive symptoms of anxiety and that this has not been researched previously. Therefore, an experimental protocol was designed in an attempt to explore this further.

It is of particular interest to preliminary investigate the CFI task, as a potential intervention in order to further understand its utility, application and efficacy in managing anxiety and panic symptoms. Given that the CO₂ challenge was administered before the CFI, the researchers wanted to determine whether administering the CFI prior to the CO₂ will change the response one has to the CO₂ challenge by comparing the physiological response from the first administration (baseline measure) to the second administration following the CFI. Furthermore, this is the first study to look at the CFI as a potential treatment intervention, a combination of qualitative research and quantitative research was decided upon to further complement this preliminary investigation.

5.7 IMPROVEMENTS OF RESEARCH PROTOCOL

Physiological data were recorded at specific intervals for each of the study conditions. In analyzing the respiration and heart rate data sets, it was noted there was variability in the physiological outcomes observed at different times post the interventions between participants, i.e., some participants had physiological changes
later than others. Hence, it was difficult to determine the best way to analyse the data set. Based on the available data recordings the data was compared 30 seconds prior to the CO₂ challenge to 30 seconds following the CO₂ challenge to be able to allow the researchers to compare the changes in mean heart rate. The sampling period prior to CO₂ was limited to 30 seconds for some participants because of technical issues, hence this sampling period was applied consistently across the cohort. Individual data for each participant was visually inspected and this also informed the time period over which physiological data were measured pre and post the conditions. This was partly informed by the literature, which suggests that the CO₂ challenge elicits a brief but strong respiratory response accompanied by neurovegetative symptoms (Griez et al., 1987; Griez & van den Hout, 1982; van den Hout & Griez, 1984). Hence in the second study investigating the effects of cold facial on CO₂ sensitivity and anxiety/panic symptoms, it was decided to extend the sampling period until 60 seconds post study conditions.

In the preliminary study, a pulse oximeter was used to measure oxygen saturation (SaO₂) levels in the blood. The pulse oximeter was worn on the index finger, and samples at a frequency of 60hz (60 samples per minute). This was used during the CFI task, however, this was discontinued as it was difficult to record the SaO₂ levels and the HR on a second to second basis from the pulse oximeter. Recording SaO₂ levels proved to be difficult and did not yield reductions in SaO₂ during the CFI task which lasted approximately 30 seconds. Hence the use of the pulse oximeter was ceased early on in the first study. Furthermore, the researchers decided that SaO₂ was beyond the scope of the research questions for the study and hence did not warrant measuring. Based on the findings of the preliminary study, the
second study had a slightly modified design, in an attempt to ameliorate the protocol of the experimental design. The pulse oximeter in the second study was re-introduced to verify the heart rate recorded on the Zephyr Bioharness, as a cross reference check before undertaking each CO₂ challenge and the CFI tasks. Whilst it was not intended for SaO₂ levels to be included in the data analysis, it was introduced as an aid for the researcher to cross-reference that the equipment was properly secured on the participants and recording accurately.

Another problem identified in the preliminary study was the difficulty some participants experienced with taking a maximal deep inhalation during the CO₂ challenge. Although participants were instructed to take a maximal deep inhalation when breathing in the 35% CO₂ and 65% O₂ gas mixture, there were varying degrees of inhalation observed between participants as discussed earlier. Given there were a number of constraints including time, resources and equipment available at Swinburne University, an alternative strategy was employed for the second study. The participant’s in the second study were instructed participant to take a maximal deep inhalation prior to the CO₂ challenge, in order to compare if the maximal deep inhalation taken during the CO₂ challenge, is comparable to the previous maximal deep inhalation breath taken.

In the preliminary study, the use of medication was exclusionary because numerous antidepressant and anxiolytic drugs may significantly reduce the response to the CO₂ challenge. In order to improve the sample size in the second study, the researcher proposed to the Ethics Committee to allow the intermittent use of painkillers and anxiolytics such as benzodiazepines, as long as they have not taken
any of these medications for at least 3 days prior to their participation in the research study. If participants were not able to achieve 3 days of abstinence of the intermittent use of medications, they were excluded or testing time was rescheduled.

Hence the main improvements for the next study included:

- Recording physiological data from 30 secs prior to 60 seconds post conditions
- Clearer instructions for participants regarding taking in a maximal inhalation prior to commencing the experimental conditions. Participants were also required to practice one maximal inhalation breathing in room air. This allowed the researcher to have a comparison point and assess whether participants were having difficulty in taking in the maximal inhalation of CO₂.
- More flexible exclusion criteria to include some medications and comorbidities of other anxiety disorders and depression. These comorbidities resulted in potential participants being excluded in the preliminary study.
Chapter 6

STUDY 2. THE EFFECTS OF COLD FACIAL IMMERSION ON CO₂ SENSITIVITY

6.8 AIM

This study aims to further investigate the applications of the diving response (DR) for panic disorder (PD) and more specifically determine whether CFI has a preventative effect on panic-related symptoms and cognition. This study comprises two phases, the first of which specifically examines the applications of the DR and cold facial immersion (CFI) in altering CO₂ sensitivity in participants with PD. The second phase of this study is a qualitative exploration of the current strategies used by clinical participants to manage anxiety and panic symptoms as well as the challenges they experience in managing their symptoms. The qualitative study also explores all participants’ experience of CFI as well as barriers and enablers to the therapeutic use of this technique among people with PD. The qualitative exploration is presented in Chapter 7.

6.9 HYPOTHESES

6.9.1 Hypothesis 1

Cold facial immersion (CFI) will reduce clinical and control participants’ sensitivity to CO₂ as evidenced by heart rate (HR) and respiration rate (RR) reductions following the subsequent CO₂.
6.9.2 Hypothesis 2

Participants in both groups will report a reduction in anxiety symptoms following CFI and subsequent CO₂ when compared to pre-measures and the CO₂ administration without CFI.

6.10 METHOD

6.10.1 Participants

A total of 36 participants were recruited to participate in this study. Of these three participants chose to discontinue, and three were excluded from being able to participate as part of the clinical group during the initial screening stage of the study. Of the participants that withdrew from the study out, two were screened into the clinical group and one into the control group. The two clinical participants chose to discontinue after experiencing discomfort with the CO₂ inhalation, and the control participant chose to discontinue after his partner in the clinical group withdrew from the study. The other three participants who were excluded from the study met the criteria for a diagnosis of PD, however one was taking medication within the exclusion criteria, and two did not meet the criteria for PD and had other co-morbidities, and hence on this basis, all three participants were excluded from the study. Sample size calculations were not possible as the response to CO₂ and CFI has not previously been investigated among people with PD. Therefore, we recruited as many participants as possible within the time and budget constraints of this PhD research study. Due to difficulties with recruitment with regard to participants who could meet the criteria for inclusion into the clinical group, 5 clinical participants who participated in the preliminary and expressed interest in being involved in further
research were invited back to participate in within the clinical group of this study. Hence the final clinical and control samples for Study 2 comprised 30 participants: 15 participants with a primary diagnosis of panic disorder (PD) with or without agoraphobia (DSM-V) (Clinical Group 1), and 15 controls who did not meet criteria for PD or mental illness (Control Group 2). Of the 30 participants, 15 were male, and 15 were females. The participants in the clinical group had an average age of 36.3 years (SD = 13.8), whilst the participants in the control group had an average age of 33.1 years (SD = 7.7). Both groups comprised 6 males and 9 females. Given that there were recruitment challenges, participants were matched as closely as possible. Demographic and clinical data for all participants are reported in the results section of this chapter.

6.10.2 Participant Sampling and Screening

Health screening assessments were carried out to establish medical eligibility to undergo the CO₂ challenge. Potential participants for both the clinical and control groups also underwent a clinical interview to assess participants against the inclusion and exclusion criteria as described in Chapter 4.

However, for the exclusion criteria regarding co-morbidities with Axis I Disorders, as measured by the DSM-V (APA, 2013), was adjusted. The exclusion criteria included all other comorbidities with the exception of another anxiety disorder and depression being secondary to the panic disorder (PD). Depression, Generalised Anxiety Disorder, and Social Anxiety Disorder were amongst the most popular comorbidities found in our study, so it was decided that if these were secondary to
PD, that they will be included. Such comorbid disorders were diagnosed by the researcher who was a clinical psychologist that was secondary to PD.

### 6.10.3 Recruitment

Participants for both the clinical group and control group were recruited as described in Chapter 4. To increase the likelihood of recruiting more clinical participants, and to display a gesture of appreciation for the participation in the study, two movie tickets were offered to participants upon completion of the study.

### 6.10.4 Measures

All participants were required to complete a battery of psychological assessments at three time points throughout the study. Descriptions of the psychological measures utilized in this study are described in Chapter 4. Table 10 provides a list of the battery of psychological measures and the time points at which the measures were administered throughout the study. Physiological measures including heart rate and respiration rate were also recorded at various points throughout the study.
Table 10.

Battery of Psychological Assessments Administered Before and During the Study

<table>
<thead>
<tr>
<th>Psychological Measures</th>
<th>Administrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Anxiety Sensitivity Index (ASI)</td>
<td>Time 1 (Baseline), Time 2, Time 3</td>
</tr>
<tr>
<td>2. Beck Anxiety Inventory (BAI)</td>
<td>Time 1 (Baseline), Time 2, Time 3</td>
</tr>
<tr>
<td>3. Discomfort Intolerance Scale (DIS)</td>
<td>Time 1 (Baseline)</td>
</tr>
<tr>
<td>4. State/Trait Anxiety Inventory (STAI) (A-Trait)</td>
<td>Time 1 (Baseline)</td>
</tr>
<tr>
<td>5. State/Trait Anxiety Inventory (STAI) (A-State)</td>
<td>Time 1 (Baseline), Time 2, Time 3</td>
</tr>
<tr>
<td>6. Panic Attack Cognitions Questionnaire (PACQ)</td>
<td>Time 1 (Baseline), Time 2, Time 3</td>
</tr>
<tr>
<td>7. Acute Panic Inventory (API)</td>
<td>Time 1 (Baseline), Time 2, Time 3</td>
</tr>
<tr>
<td>8. Visual Analog Scale for Anxiety (VAS) (Participant &amp;</td>
<td>Time 2, Time 3 (x 2)</td>
</tr>
<tr>
<td>Researcher)</td>
<td></td>
</tr>
<tr>
<td>9. Center for Epidemiological Studies Depression Scale</td>
<td>Time 1 (Baseline)</td>
</tr>
<tr>
<td>(CES-D)</td>
<td></td>
</tr>
</tbody>
</table>

6.10.4.1 Research Design

Participants took part in two experimental challenges including the (1) CO2 Challenge, and (2) Cold Facial Immersion Task followed by CO2 Challenge. The assignment of conditions was counterbalanced. Figure 16 displays the experimental procedure indicating when physiological and psychological (cognitive) measures were collected as part of this study.
Figure 16. Experimental procedure for data collection for Group 1 (Clinical) and Group 2 (Control) participants.
6.10.5 Procedure

The experimental study was held at a clinical room at Swinburne University, which was specifically set up for the research. A compact physiological monitoring system (Zephyr Bioharness), featuring a chest strap and external multi-recording and monitoring device was used to measure heart rate, posture, breathing wave and respiration rate. All participants undertook the challenges involved in this study whilst wearing the chest strap connected to the Zephyr Bioharness. Participants were required to undertake Time 1 and Time 2 procedures on the same day. Participants were scheduled to complete Time 3 tasks on a different day as ethics approval only allowed for participant’s to complete one CO₂ inhalation per day.

On completion of the experimental procedure for this study, participants were invited to participate in an interview in which the researcher asked clinical participants a number of qualitative questions regarding their experience of their anxiety and panic symptoms. Both clinical and control participants were also asked about their experience of the CFI task. The results of the Qualitative Study are discussed in Chapter 7.

6.10.6 Data Cleaning

Prior to statistical analyses, all variables were assessed for the presence of missing data and outliers, in accordance with the method described in Section 4.3.3.5. The data revealed missing values and hence Little’s Missing Completely at Random (MCAR) test was used to assess whether data were missing at random. Assumptions for the MCAR test were assessed and fulfilled, \( \chi^2 (39) = 46.165, DF = 39, p > .005 \). Missing values were replaced using the expectation-maximisation (EM) algorithm for
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Cold Facial Immersion and CO₂ Sensitivity

imputation. Prior to conducting statistical analyses, the distributions of all variables were visually inspected to determine if they met the assumption of normality of distribution, a requirement of parametric statistical analyses. In cases where data did not adequately meet the assumptions of normality and could not be transformed to normalise their distributions according to recommended procedures (Tabachnick & Fidell, 2007), non-parametric analyses were conducted.

6.10.7 Statistical Analyses

Prior to conducting parametric analyses, data were inspected to ensure they met assumptions for such analyses. Physiological data, including respiration rate (RR) and heart rate (HR) data, satisfied the assumptions for parametric analysis. Hence t-tests and ANOVA analyses were employed to investigate the differences between the clinical and control group on the experimental conditions. Examination of normal distribution revealed that scores across all self-report psychological measures taken at Pre-test, at Time 1 (CO₂) and Time 2 (CFI plus CO₂), including API, ASI, BAI, PACQ, STAI, VAS-R, and VAS-P did not meet the assumptions of normal distribution for parametric analyses. Hence non-parametric tests were utilised. Spearman rank-order correlation coefficient was used to investigate the relationships between the psychological measures. Friedman’s test was used to examine differences in the psychological measures collected across the experimental conditions. Demographic information was compared for Group 1 and Group 2 using Fishers. The Statistical Package for Social Sciences version 22.0 was used for all analyses.
6.11 RESULTS

6.11.1 Overview of Analysis

The analysis of this study is presented in three sections. The first section presents the comparison of demographic details between groups and the correlations of the pre-test measures. The second section reports the examination of physiological differences between the panic and control groups at Time 1 and 2. This section also reports the results of mixed ANOVAs, examining the effects of Time 1 and Time 2 tasks on the participant’s physiological responses (HR and RR). The third section examines the effects of the CO2 challenge and ultimately the effect of CFI on CO2 sensitivity across the anxiety measures. When outcomes were not normally distributed Friedman tests were used instead of ANOVA tests and Wilcoxon signed-rank tests were used instead of paired t-tests.

6.11.2 Correlations between Pre-measures

No significant differences (p = .44) in age were observed between the clinical (M = 36.3 years, SD = 13.8) and control groups (M = 33.1 years, SD = 7.7). Tables 11 and 12 provide a comparison for the clinical and control groups. In examining the demographic information in Study 2, significant differences were observed between groups in education level and gardening. Participants were matched for age and gender as closely as possible.
### Table 11

**Demographic Information Categorical Data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (Clinical)</th>
<th>Group 2 (Controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fisher’s z,</td>
<td>N</td>
</tr>
<tr>
<td>Gender</td>
<td>$p = 1.000$</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Education Level</td>
<td>$p = .005$</td>
<td></td>
</tr>
<tr>
<td>No University Degree</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>University Degree</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Employment Status</td>
<td>$p = .008$</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Unemployed/Student</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Smoking</td>
<td>$p = .651$</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Drinking</td>
<td>$p = .050$</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Physical Fitness</td>
<td>$p = .1000$</td>
<td></td>
</tr>
<tr>
<td>Poor/Fair</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Good/Very Good</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Physical Activity at Work</td>
<td>$p = .715$</td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Non-sedentary</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Employment status</td>
<td>$p = 1.000$</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Employed/Student</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Weekly Physical Exercise</td>
<td>$p = .206$</td>
<td></td>
</tr>
<tr>
<td>&lt; 3 hrs</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>&gt; 3 hrs</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Weekly Cycling</td>
<td>$p = 1.000$</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Some</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Weekly Walking</td>
<td>$p = 1.000$</td>
<td></td>
</tr>
<tr>
<td>&lt; 3 hrs</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>&gt; 3 hrs</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Weekly home duties</td>
<td>$p = 1.000$</td>
<td></td>
</tr>
<tr>
<td>&lt; 1 hr</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>&gt; 3 hrs</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Weekly gardening</td>
<td>$p = .035$</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Some</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Walking Pace</td>
<td>$p = 1.000$</td>
<td></td>
</tr>
<tr>
<td>Slow/Steady, average</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Brisk pace/Fast&gt;6km</td>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>

*Note. N = 30 (group 1: n = 15, group 2: n = 15). p-values from Fisher’s exact test (2-sided).*
Table 12.

**Demographic Information Continuous Data**

<table>
<thead>
<tr>
<th></th>
<th>Panic M</th>
<th>SD</th>
<th>Controls M</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water Comfort (Mann-Whitney, p=.933)</td>
<td>7.70</td>
<td>1.87</td>
<td>7.40</td>
<td>2.82</td>
</tr>
<tr>
<td>(0 = Not at all comfortable - 10 = Very comfortable)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average No. of Glasses per week (Mann-Whitney, p=.270)</td>
<td>2.23</td>
<td>3.42</td>
<td>2.73</td>
<td>2.93</td>
</tr>
<tr>
<td>No. Push Ups (Mann-Whitney, p=.443)</td>
<td>9.93</td>
<td>6.64</td>
<td>15.73</td>
<td>14.42</td>
</tr>
<tr>
<td>Height (Mann-Whitney, p=.406)</td>
<td>168.07</td>
<td>7.56</td>
<td>169.40</td>
<td>11.21</td>
</tr>
<tr>
<td>Weight (Mann-Whitney, p=.604)</td>
<td>71.40</td>
<td>11.78</td>
<td>71.33</td>
<td>22.96</td>
</tr>
</tbody>
</table>

Note. P-values are based on Mann-Whitney test (2 sided)

The Spearman rank-order correlation coefficient was used as a nonparametric measure to determine the strength and direction of association that exists between the pre-measure assessments. Correlation coefficients between pre-measure assessments are presented in Table 13.

A series of t-tests for independent groups was employed to determine if significant differences existed between the clinical and the control group on the scores of all psychological measures at the pre-test stage. The results of the analysis indicated that there were significant differences (p < .05) across all psychological measures at pre-test with the exception of the DIS which was not significant at (p > .05). The DIS is a measure of discomfort intolerance rather than anxiety.
Table 13:

**Correlations between Pre-measure Assessments**

<table>
<thead>
<tr>
<th></th>
<th>PACQ</th>
<th>BAI</th>
<th>CESD</th>
<th>STAI-T</th>
<th>ASI</th>
<th>STAI_S</th>
<th>API</th>
<th>DIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACQ</td>
<td>1.00</td>
<td>.865**</td>
<td>.760**</td>
<td>.847</td>
<td>.792**</td>
<td>.734**</td>
<td>.656</td>
<td>.405</td>
</tr>
<tr>
<td>BAI</td>
<td>1.00</td>
<td></td>
<td>.719**</td>
<td>.744**</td>
<td>.813**</td>
<td>.602</td>
<td>.663</td>
<td>.422</td>
</tr>
<tr>
<td>CESD</td>
<td>1.00</td>
<td></td>
<td></td>
<td>.847**</td>
<td>.798**</td>
<td>.734**</td>
<td>.486</td>
<td>.219</td>
</tr>
<tr>
<td>STAI-T</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td>.745**</td>
<td>.756**</td>
<td>.678</td>
<td>.164</td>
</tr>
<tr>
<td>ASI</td>
<td>1.00</td>
<td>.734</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.559</td>
<td>.331</td>
</tr>
<tr>
<td>STAI-S</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.726**</td>
<td></td>
<td></td>
<td>.313</td>
</tr>
<tr>
<td>API</td>
<td>1.00</td>
<td>.403</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

Note. N = 30. ** p < .001

6.11.3 Physiological Differences at Time 2 (CO₂ Challenge) and Time 3 (Cold Facial Immersion + CO₂ Challenge)

A mixed, ANOVA was conducted to compare the panic and control group in terms of the effect of the CO₂ challenge task and group on participants’ RR. Table 14 shows respiration rate means and standard deviations for all participants before and after the CO₂ Challenge (Time 2) and before and after the CFI + CO₂ Task (Time 3)
Table 14

**Descriptive Statistics for Respiration Rate (RR) before and after Time 2 (CO₂) and before and after Time 3 (CFI + CO₂)**

<table>
<thead>
<tr>
<th>Group</th>
<th>RR Time 2 (b CO₂)</th>
<th>RR Time 2 (p CO₂)</th>
<th>RR Time 3 (b. CFI + CO₂)</th>
<th>RR Time 3 (p. CFI + CO₂)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>14.60</td>
<td>3.08</td>
<td>15.90</td>
<td>3.59</td>
</tr>
<tr>
<td></td>
<td>15.30</td>
<td>3.03</td>
<td>16.95</td>
<td>3.59</td>
</tr>
<tr>
<td></td>
<td>14.40</td>
<td>2.64</td>
<td>15.52</td>
<td>4.30</td>
</tr>
<tr>
<td></td>
<td>14.34</td>
<td>2.41</td>
<td>16.32</td>
<td>4.21</td>
</tr>
</tbody>
</table>

There was no significant interaction between the effects of group and CO₂ challenge task on participant’s RR, \((F = (1, 28) = .706, p = 0.38, \eta^2 =.005)\). Simple main effects analysis showed that between 30 seconds prior to the CO₂ challenge (Time 2) and 60 seconds following the CO₂ challenge (Time 3), participant’s experienced no significant change in respiration rate, \((F = (1, 28) = 3.549, p = .070, \eta^2 =.112)\). There were no significant differences in respiration rates observed between the clinical and control group, \((F(1, 30) = 1.704, p = .20, \eta^2=.057)\).

A mixed, ANOVA was also conducted to compare the panic and control group in terms of the effect of the CO₂ challenge task and group on participants’ HR. Table 15 shows heart rate means and standard deviations for all participants before and after the CO₂ Challenge (Time 2) and before and after the CFI + CO₂ Task (Time 3).
Table 15

**Descriptive Statistics for Heart Rate (HR) before and after Time 2 (CO2) and after Time 3 (CFI + CO2)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Clinical (n = 15)</th>
<th>Control (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>HR Time 2 (b CO2)</td>
<td>95.37</td>
<td>16.02</td>
</tr>
<tr>
<td>HR Time 2 (p CO2)</td>
<td>97.96</td>
<td>20.79</td>
</tr>
<tr>
<td>HR Time 3 (b. CFI + CO2)</td>
<td>100.31</td>
<td>19.08</td>
</tr>
<tr>
<td>HR Time 3 (p. CFI + CO2)</td>
<td>92.92</td>
<td>10.97</td>
</tr>
</tbody>
</table>

Furthermore, no significant interaction was found between the effects of group and CO2 on participant’s HR, \( F(1, 28) = 1.028, \ p = .319, \ \eta^2 = .035 \). Simple main effects analysis showed that between 30 seconds prior to the CO2 challenge and 60 seconds following the CO2 challenge at Time 2, the participants experienced no significant change in heart rate, \( F(1, 28) = .003, \ p = .955, \ \eta^2 = .000 \). There were also no significant differences between heart rates observed between the clinical and control group, \( F(1, 28) = .489, \ p = .490, \ \eta^2 = .017 \).

Further mixed ANOVA analyses were conducted to compare the groups in terms of the effects of CFI, specifically at Time 2 (CO2 challenge) and Time 3 (CFI plus CO2 challenge), on participants’ heart rate (HR). A mixed ANOVA was conducted with the clinical and control group to examine the effect of CFI on participants’ HR and examine whether differences between groups were observed. There were no significant interaction between the effects of group and CFI on participant’s HR, \( F(1, 28) = .074, \ p = .787, \ \eta^2 = .003 \). Simple main effects analysis
showed that between at Time 3, at the start and end of the CFI task (prior to the CO2 Challenge), participant’s experienced a significant heart rate reduction, \( F(1, 28) = 121.492, p =< 0.01, \eta^2=.813 \) (see Figure 17). However no significant differences between the clinical and control group were observed, \( F(1, 28) = 2.902, p = .100, \eta^2=.094 \).

![Graph](image)

**Figure 17.** Mean Heart Rate (SE) for all participants (clinical n = 15, and control n = 15) pre and post the Cold Facial Immersion before CO2 at Time 3.

### 6.11.4 Psychological Measures and Effect of CFI on CO2 Sensitivity

Mann Whitney U test was used to examine differences in the psychological measures collected across the three time periods. The clinical group has significantly higher scores compared to the control group on all psychological measures at Time 1 (Pre-test) and Time 2 (CO2) \( p<0.05 \). At Time 3 (CFI after CO2) the clinical group was significantly higher on all psychological measures \( p<0.05 \), with the exception of the STAI (State) \( p = .106 \), and VAS- Participant ratings \( p=.116 \).
Table 16 provides medians for all self-report psychological measures taken at Time 1 (Pre-measures), Time 2 (CO₂), and Time 3 (CFI plus CO₂).

**Table 16. Medians, Minimum, Maximum and Interquartile Ranges for Psychological Measures at Time 1, Time 2 and Time 3.**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mdn</th>
<th>Min</th>
<th>Max</th>
<th>Interquartile Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Panic Inventory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1 (Pre-test)</td>
<td>1</td>
<td>0</td>
<td>31</td>
<td>2.25</td>
</tr>
<tr>
<td>Time 2 (p. CO₂)</td>
<td>7.5</td>
<td>0</td>
<td>42</td>
<td>13.25</td>
</tr>
<tr>
<td>Time 3 (p.CFI + CO₂)</td>
<td>2.5</td>
<td>0</td>
<td>23</td>
<td>5.25</td>
</tr>
<tr>
<td><strong>Anxiety Sensitivity Index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1 (Pre-test)</td>
<td>33.5</td>
<td>17</td>
<td>73</td>
<td>28</td>
</tr>
<tr>
<td>Time 2 (p. CO₂)</td>
<td>34</td>
<td>16</td>
<td>80</td>
<td>27.5</td>
</tr>
<tr>
<td>Time 3 (p. CFI + CO₂)</td>
<td>27</td>
<td>17</td>
<td>63</td>
<td>24</td>
</tr>
<tr>
<td><strong>Beck Anxiety Inventory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1 (Pre-test)</td>
<td>11.5</td>
<td>0</td>
<td>61</td>
<td>23.75</td>
</tr>
<tr>
<td>Time 2 (p. CO₂)</td>
<td>19.5</td>
<td>0</td>
<td>62</td>
<td>21.5</td>
</tr>
<tr>
<td>Time 3 (p. CFI + CO₂)</td>
<td>6</td>
<td>0</td>
<td>34</td>
<td>11.25</td>
</tr>
<tr>
<td><strong>Panic Cognitions Questionnaire</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1 (Pre-test)</td>
<td>10.5</td>
<td>0</td>
<td>68</td>
<td>31</td>
</tr>
<tr>
<td>Time 2 (p. CO₂)</td>
<td>4</td>
<td>0</td>
<td>75</td>
<td>18</td>
</tr>
<tr>
<td>Time 3 (p. CFI + CO₂)</td>
<td>2</td>
<td>0</td>
<td>27</td>
<td>12.25</td>
</tr>
<tr>
<td><strong>State Anxiety Inventory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1 (Pre-test)</td>
<td>28.5</td>
<td>20</td>
<td>61</td>
<td>21.25</td>
</tr>
<tr>
<td>Time 2 (p. CO₂)</td>
<td>39.5</td>
<td>20</td>
<td>74</td>
<td>28.25</td>
</tr>
<tr>
<td>Time 3 (CFI + CO₂)</td>
<td>30</td>
<td>20</td>
<td>68</td>
<td>20.5</td>
</tr>
<tr>
<td><strong>VAS – Participant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1 (p. CO₂)</td>
<td>5</td>
<td>0</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Time 2 (p. CO₂ b. CFI)</td>
<td>0.5</td>
<td>0</td>
<td>5</td>
<td>2.13</td>
</tr>
<tr>
<td>Time 3 (p. CFI + CO₂)</td>
<td>3</td>
<td>0</td>
<td>8</td>
<td>4.13</td>
</tr>
<tr>
<td><strong>VAS – Researcher</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1 (p. CO₂)</td>
<td>5</td>
<td>0</td>
<td>10</td>
<td>5.5</td>
</tr>
<tr>
<td>Time 2 (p. CO₂ b. CFI)</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Time 3 (p. CFI + CO₂)</td>
<td>2.5</td>
<td>0</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>

*Note. N = 30 (group 1: n =15, group 2: n = 15).*
API ratings were significantly different across the three times, $\chi^2(2) = 28.404$, $p < .001$. Post-hoc analysis with Wilcoxon signed-rank tests were conducted with a Bonferroni correction applied, resulting in a significance level set at $\alpha = p < 0.017$. The median API ratings were 1.0 at Time 1, 7.5 at Time 2, and 2.5 at Time 3. A significant increase was seen between Time 1 and Time 2, ($Z = -4.401$, $p < .001$). A significant decrease was observed between Time 2 and Time 3, ($Z = 3.235$, $p = .001$). There were no significant differences between the participants’ baseline API measures and those taken at time 3 following the CO$_2$ challenge, ($Z = -.1651$, $p > .017$). Figure 18 displays a box plot of participants’ API scores measured at baseline (Time 1), following the CO$_2$ challenge (Time 2), and after the CFI and CO$_2$ challenge (Time 3).

Figure 18. Median and interquartile range for API scores for all participants (clinical and control group (N=30) at Time 1*, Time 2*, and Time 3* (*p < .05).
ASI ratings were significantly different across the three times, $\chi^2(2) = 17.741$, $p < 0.01$. Post-hoc analysis with Wilcoxon signed-rank test was conducted with a Bonferroni correction applied, resulting in a significance level set at $\alpha = p < 0.016$. The median ASI ratings were 33.5 at Time 1, 34 at Time 2, and 27 at Time 3. No significant difference was observed between baseline (Time 1) and Time 2, ($Z = 0.520, p > 0.017$), whilst a significant decrease was noted between Time 2 and Time 3, ($Z = 2.654, p = 0.008$). A significant decrease was also observed between Time 1 and Time 3, ($Z = -3.019, p = 0.003$). Figure 19 displays a box plot of participants’ ASI scores measured at baseline (Time 1), following the CO$_2$ challenge (Time 2), and after the CFI and CO$_2$ challenge (Time 3).

![Figure 19](image_url)

*Figure 19. Median and interquartile range for ASI scores for all participants (clinical and control group) (N=30) at Time 1*, Time 2*, and Time 3* ($p < .05$).
BAI ratings were significantly different across the three times, $\chi^2(2) = 14.131$, $p = .001$. Post-hoc analysis with Wilcoxon signed-rank test was conducted with a Bonferroni correction applied, resulting in a significance level set at $\alpha = p < .017$. The median BAI ratings were 11.51 at Time 1, 19.5 at Time 2, and 6.0 at Time 3. No significant difference was noted between Time 1 and Time 2 ($Z = -1.211$, $p > .017$). A significant decrease was seen between Time 1 and Time 3, ($Z = -3.607$, $p < .001$). A significant decrease was observed between Time 1 and Time 3, ($Z = -2.849$, $p = .004$). Figure 20 displays a box plot of participants’ BAI scores measured at baseline (Time 1), following the CO₂ challenge (Time 2), and after the CFI and CO₂ challenge (Time 3).

![Box plot of BAI scores](image)

*Figure 20. Median and interquartile range BAI scores for all participants (clinical and control group (N=30) at Time 1*, Time 2*, and Time 3* (p < .05).
PACQ ratings were significantly different across the three times, \( \chi^2(2) = 12.896, p = .002 \). Post-hoc analysis with Wilcoxon signed-rank test was conducted with a Bonferroni correction applied, resulting in a significance level set at \( \text{Alpha} = p < .017 \). The median PACQ ratings were 10.5 at Time 1, 4.0 at Time 2, and 2.0 at Time 3. No significant differences were observed between baseline and time 2, \( (Z = 2.234, p > .017) \), and Time 2 and Time 3 \( (Z = -2.218, p > .017) \). A significant decrease was observed between Time 1 and Time 3, \( (Z = 3.495, p < .001) \). Figure 21 displays a box plot of participants’ PACQ scores measured at baseline (Time 1), following the CO\(_2\) challenge (Time 2), and after the CFI and CO\(_2\) challenge (Time 3).

*Figure 21. Median and interquartile range for PACQ scores for all participants (clinical and control group (N=30) at Time 1*, Time 2*, and Time 3* (p < .05).
STAI ratings were significantly different across the three time periods, $\chi^2(2) = 23.078$, $p < 0.01$. Post hoc analysis with Wilcoxon signed-rank tests was conducted with a Bonferroni correction applied, resulting in a significance level set at $\text{Alpha} = p < .017$. The median STAI ratings were 28.5 at Time 1, 39.5 at Time 2, and 30.0 at Time 3. There was a significant increase between the participants’ baseline STAI measures and those taken at time 2, following the CO$_2$ challenge, ($Z = -.4.159$, $p < .001$). A statistically significant decrease was seen between Time 2 and Time 3, ($Z = -3.305$, $p = .001$). There was no significant difference between Time 1 and Time 3, ($Z = -0.833$, $p > .017$). Figure 22 displays a box plot of participants’ STAI-S scores measured at baseline (Time 1), following the CO$_2$ challenge (Time 2), and after the CFI and CO$_2$ challenge (Time 3).

![Figure 22](image)

*Figure 22. Median and interquartile range for STAI scores for all participants (clinical and control group (N=30) at Time 1*, Time 2*, and Time 3* (* $p < .05$).*
Chapter 6  Cold Facial Immersion and CO2 Sensitivity

VAS Participant ratings were significantly different across the three times, \( \chi^2(2) = 28.055, p < 0.01 \). Post-hoc analysis with Wilcoxon signed-rank test was conducted with a Bonferroni correction applied, resulting in a significance level set at Alpha = p < .017. The median VAS-P ratings were 5.0 at Time 1, 0.5 at Time 2, and 3.0 at Time 3. Significant decreases were observed between baseline and Time 2, \( (Z = -4.363, p < .001) \), and between Time 2 and Time 3, \( (Z = -3.782, p < .001) \). Furthermore, a significant decrease was seen between Time 1 and Time 3, \( (Z = -2.801, p = .005) \). Figure 23 displays a box plot of participants’ VAS Participant scores measured at baseline (Time 1), following the CO2 challenge (Time 2), and after the CFI and CO2 challenge (Time 3).

![Box plot](image)

**Figure 23.** Median and interquartile range for VAS – Participant scores for all participants (clinical and control group (N=30) at Time 1*, Time 2*, and Time 3* (p<.05)
VAS Researcher ratings were significantly different across the three times, \( \chi^2(2) = 39.086, p < 0.01 \). Post-hoc analysis with Wilcoxon signed-rank test was conducted with a Bonferroni correction applied, resulting in a significance level set at Alpha = p < .017. The median VAS-R ratings were 5.0 at Time 1, 0 at Time 2, and 2.5 at Time 3. A significant decrease was seen between baseline and Time 2, (Z = -4.462, p < .001), and between Time 2 and Time 3, (Z = 4.178 p < .001). Furthermore, there was a significant decrease between Time 1 and Time 3, (Z = -3.506, p < .001). Figure 24 displays a box plot of VAS Researcher scores measured at baseline (Time 1), following the CO\(_2\) challenge (Time 2), and after the CFI and CO\(_2\) challenge (Time 3).

Figure 24. Median and interquartile range for VAS-Researcher scores for all participants (clinical and control group (N=30) at Time 1*, Time 2*, and Time 3* (p < .05).
6.12 DISCUSSION

The principal findings of this study were that there were no differences in heart rate (HR) and respiration rate (RR) within or between groups in response to the CO₂ challenge. Following the CO₂ challenge, the clinical group was observed to have more elevated anxiety and panic symptoms, as reported by the anxiety measures in comparison to the control group. Furthermore, a significant reduction in anxiety symptomatology was observed in both the clinical and control group following the cold facial immersion (CFI). The results of this study are consistent with the finding of the preliminary study and are discussed in light of the novel hypotheses in this study.

Hypothesis 1: It was expected that the CFI task will reduce CO₂ sensitivity as evidenced by HR and RR reductions following the subsequent CO₂ challenge in clinical and control participants. The findings did not provide support for this hypothesis as there was no significant difference found in participants’ HR and RR between Time 2 (CO₂ challenge) and Time 3 (CFI and CO₂). However, the results examining the effects of the CFI task (prior to the administration of CO₂) indicate a significant reduction in HR for both clinical and control participants. In line with the preliminary study findings, these results indicate that CFI has anxiolytic effects. However, despite its powerful response, it cannot be inferred that one single administration of CFI can alter one’s sensitivity to CO₂.

Hypothesis 2: It is hypothesised that following the CFI and subsequent CO₂ challenge, all participants will report a reduction in anxiety in comparison to pre-measures and the CO₂ administration without CFI. This hypothesis was supported as
there was a significant reduction noted between Time 1 (baseline pre-measures) and Time 3 (CFI plus CO₂) on the following anxiety measures Anxiety Sensitivity Index (ASI), State and Trait Anxiety Inventory STAI, Panic Attack Cognitions Questionnaire (PACQ), Beck Anxiety Inventory (BAI), Visual Analogue Scale completed by the participant (VAS-P) and researcher (VAS-R), with the exception of Acute Panic Inventory (API) for the both the clinical and control groups. Furthermore, significant decreases in anxiety symptoms were reported from Time 2 (CO₂) to Time 3 (CFI plus CO₂) on the following measures; API, ASI, BAI, STAI, VAS-R, and VAS-P, with the exception of the PACQ which was not found to change significantly between Time 2 and 3. A possible explanation for this finding may have been that control participants did not have panic cognitions in response to the CO₂ challenge. Whilst the control group has minimal symptoms overall in response to the CO₂ challenge, they did report a reduction in symptoms and calming effects in response to the CFI task. The clinical group reported a decrease in anxiety symptoms, following exposure to the CFI task on all anxiety measures including the ASI, API, STAI, PACQ, BAI, VAS-R and VAS-P. The reduction observed in anxiety symptoms warrant further investigation to examine whether frequent exposure to the CFI tasks and to breath-holding may be able to reduce CO₂ sensitivity in PD patients over time. Practicing breath-holding and activating the diving response (DR) through free diving and CFI on a regular basis has been known to have trained effects, subsequently reducing CO₂ sensitivity (Konstandinidou & Chairopoulou 2017). Reports in the literature have suggested that a blunted hypercapnic response and prolonged breath-hold times have been associated with the benefits of trained effects and repeated apneas (Andersson & Schagatay, 2009; Walterspacher et al., 2011; Roecker et al., 2014, Grassi et al., 1994; Foster & Sheel, 2005). Goosens et al. (2014)
in their study found that experienced divers displayed a decreased behavioural response to CO₂ as compared to clinical participants with PD and healthy controls. This finding is also consistent with the research of Earing et al. (2014), who found that experienced divers possess a lower ventilatory response to CO₂ suggesting a strong adaptation of central CO₂ sensitivity.

Whilst the current study was unable to identify whether one single administration of the CFI task can alter CO₂ sensitivity, further investigation of this novel intervention is warranted given the observed significant reductions in self-reported anxiety symptoms and heart rate for both clinical and control participants.

6.12.1 Study Limitations

There were various limitations in the current study, with some similarities shared with the preliminary study. Recruiting participants for the clinical group was challenging due to a low number of participants applying. As a result, the researcher invited five participants from the preliminary study to participate. These participants had expressed interest in being involved in more research in this area. Despite having more flexible exclusion criteria in this study, the recruitment of clinical participants proved to be more difficult than the preliminary study. For example, in Study 2 participants with intermittent use of benzodiazepines, anxiolytics and painkillers were allowed to participate in the study and we extended the age from 55 years of age to 60 years of age, in an attempt to recruit more participants. The low number of participants made it difficult to compare groups. Furthermore, the participants in the control group were again mostly university students studying psychology. Although attempts were made in Study 2 to match participants and to recruit non-university
students as controls, this was difficult to accomplish. Hence the results may not be truly representative of what a normal population may look like.

Another limitation of the preliminary study may have been participant’s reported comfort level with water. Participants who did not feel comfortable with water may not have felt comfortable or relaxed during the CFI task. It is important to consider this in future studies, or when determining with clients alternative ways to activate the DR. This is something that we wanted to explore in the qualitative interviews further to gain a better understanding of the different preferences and possibilities of activating the DR.

A further limitation is that both the CO₂ challenge and the CFI task elicit a brief response. A drawback to this may be that participants may not accurately report what they experience as by the time they complete the self-report anxiety measures minutes later, their symptoms may have dissipated. Although the VAS-P and VAS-R were used to try to capture how anxious participants felt following the tasks, an improvement to consider would be to administer these tests at baseline before any condition as a means of comparison. Other methodological considerations for future studies investigating the CFI and the DR include improving the provocation of the CO₂ challenge, the continuous data acquisition during the experimental design, and matching participants for age and gender.

6.12.2 Methodological Considerations for Future Research

An important methodological consideration for future research is to use the standardized experimental equipment described by Schruers and colleagues (Schruers
et al., 2011) and to include maximal vital capacity inhalations: one placebo condition (normal room air) and one with CO2 enriched air. A stopcock used with two positions, one for the normal air and one for the premixed CO2, is connected to either the mouthpiece or the mask, in a way so the participant does not know which condition is being administered (Hood et al., 2006). The odour or taste associated with the CO2 is minimal, and as participants are not informed of the order of the conditions they are being administered, placebo effects can be easily identified (O'Leary, 2000). This method does not ensure a true blind as the participants do not usually respond physiologically to the placebo, and the CO2 inhalation elicits immediate effects (Ogliari et al., 2010).

The CO2 challenge proved to have some difficulties including individual variability in response to the CO2 challenge. Some participants complained of the taste and were not able to hold the inhaled gas mixture for a duration of 4 seconds which they were instructed to do before exhalation. Clinical participants may have also been fearful of the CO2 provocation method used and its potential to elicit a panic attack, hence they approached the single breath inhalations with a degree of apprehension. Furthermore, if they were unsuccessful in breathing in the CO2 by taking in a maximal deep inhalation and holding the breath for a count of 4 seconds, the researcher was unable to re-administer the CO2, as ethics approval was only granted for one maximum CO2 inhalation per participant per day.

Furthermore, some participants reported difficulties with being able to breathe in the CO2 properly, which resulted in an inability to take in a deep maximal inhalation. Reports in the literature suggest that more sophisticated methods have
been used, including standardised experimental equipment developed by Schruers and colleagues (Schruers et al., 2011). This involves either a mask or a combination of a mouthpiece and a nose clip which aids the participant to receive a maximal vital capacity inhalation. Also recording devices such as the Finapress recorder are commonly used to record continuous HR measurement (Vickers et al., 2012). In the current study, the equipment we used was limited to that available at the university.

The provocation method used in our study may have been more appropriate for investigating a more restricted, but perhaps more homogeneous, phenotype within the wider clinical domain of PD syndromes (e.g., the respiratory subtype group of PD) (Smoller & Tsuang, 1998). There is no consensus with some research favouring (Battaglia, 2002; Battaglia, et al., 2001) and others questioning (Gorman et al., 2000) the utility of CO₂ in informing central nervous system mechanisms connected to suffocation and PD. In this preliminary study, it would have been interesting to recruit and compare both the respiratory and non-respiratory PD subtypes to investigate differences in how the groups vary in their response to the provocation methods (i.e., BH tasks, 35% CO₂ challenge and CFI task). Future studies may investigate differences between the respiratory and the non-respiratory clinical group.

Future research should consider gathering continuous cardiorespiratory data recorded from start to finish, to include data between conditions, using a physiological recording device such as the Zephyr Bioharness Bluetooth device, used in this study, to capture the relevant data. This may assist with identifying at what time periods the most significant cardiorespiratory changes occurred. Another consideration for future studies may be for the researcher and the participant to complete the Visual Analog
Scale (VAS) following each task of all conditions, which include both breath-hold tasks, both CO₂ challenges and following the CFI task, as a way of comparison. This may yield important information regarding how anxious participants are likely to feel following both breath-hold-tasks (Condition A) and following the CFI (Condition B). This would allow for the (CFI) task (Condition B) to be compared with the CO₂ Challenge + CFI task (Condition D), with respect to the VAS researcher and participant ratings. Furthermore knowing how anxious or relaxed a participant is feeling, following these abovementioned conditions, may yield important information regarding how they may respond to the next randomly assigned challenge or task, as well as information regarding their cardiorespiratory response.

6.12.3 Future Directions

Schagatay and Andersson (1998) suggested that the DR can be trained and that it can elicit benefits on both HR reduction and apnoeic duration. It appears plausible that PD individuals may have benefited from achieving trained effects of the DR through the regular use of apnea training and CFI, as observed in free divers. According to Christoforidi et al. (2012) the parasympathetic branch and resting cardiac autonomic activity was increased in free divers compared to untrained participants as evidenced by significantly lower minimum and mean heart rate. Vagal tone and resting cardiac autonomic adaptation are different in free divers because of known trained effects (Christoforidi et al., 2012). Park and Thayer (2014) posit that cardiac vagal tone also known as heart rate variability facilitates effective emotion regulation as it is associated with more “adaptive and functional top-down and bottom-up cognitive modulation of emotional stimuli” (p.1). Free divers are a unique
group that possess excellent mental control, and exceptional breathing control to be able to reach depths that were beyond imaginable.

Furthermore, reports in the literature suggest a clear link between respiratory disorders and PD (Biber & Alkin, 1999; Nardi et al., 2002, 2006a, 2006b; Freire et al., 2008; Papp et al., 1989; Valenca et al., 2002). Joulia et al. (2009), postulated that apnea training provided hypoxic preconditioning and hence it may be potentially used to optimise hypoxia protection in patients with respiratory conditions such as chronic obstructive pulmonary disease and asthma. Breathing exercises used by free divers such as pranayama yoga, square and triangular breathing which involve inhaling, exhaling and breath-hold (i.e., for 3 seconds each) have been associated with deeper states of relaxation (Mana, 2010). Jerath et al. (2006) have demonstrated multiple benefits including decreased oxygen consumption, heart rate, and blood pressure, as well as increased theta wave amplitude in EEG recordings, and parasympathetic activity as a result of regular use of pranayama yoga breathing. Experiences of alertness and reinvigoration have also been reported by regular users (Jerath et al., 2006).

A study by Schagatay et al. (2000) demonstrated that both frequent exposure and apnea performance increase breath-hold (BH) time, by delaying the physiological breaking point and enhancing bradycardia. According to Schagatay and Anderrson (2009), future research should investigate the time course for the development of the trained effects, specifically how frequent and how many apnea exposures are required. This warrants further investigation, in order to explore the benefits of breath-hold training (BHT) and CFI in the treatment of PD. Understanding the
physiological adaptations of apnea training, and the techniques used in the sport of freediving, including the activation of the DR, may shed some light into the development of novel and innovative treatments used to treat and manage panic and anxiety symptoms.

The CFI task may also be used as a diagnostic tool to inform the clinician of the patient’s suffocation alarm system, and breathing irregularities. Imperatively, it may also be used as a proposed intervention, psycho-educationally and as a behavioural experiment with clinical participants to reduce panic symptoms and cognitions. Moreover, in a behavioural experiment, the CFI task can be applied following a hyperventilation challenge in an attempt to reverse the physiological symptoms of anxiety and to help challenge and correct the erroneous beliefs and panic cognitions. According to Barlow and Craske (2014), voluntary hyperventilation is a way to expose patients with PD to sensations associated with panic and to activate catastrophic cognitions that need restructuring. Given the calming effects of the CFI and the reduction in physiological symptoms and cognitive symptoms of panic and anxiety, the CFI may be used following a hyperventilation exercise to regulate the autonomic nervous system and to counteract catastrophic cognitions.

CBT may also be able to draw on the adaptation of the DR to counteract anxiety sensitivity erroneous beliefs. A large body of research has demonstrated a relationship between anxiety sensitivity and panic-related psychopathology and have suggested that anxiety sensitivity often precedes the development of PAs (Bouton et al., 2001; Dixon, Sy, Kemp & Deacon, 2013; McNally, 1994, 2000; Reiss, 1991; Poletti et al., 2015; Reiss & McNally, 1985, Semidt, Lenew & Jackson, 1997; Taylor,
1995). According to Barlow, (1988, 2002), Craske & Barlow, (2013) and Gallagher et al. (2013) correcting erroneous beliefs via CBT interventions such as cognitive restructuring and the use of behavioural experiments have demonstrated a reduction in anxiety-related symptoms. The design and implementation of behavioural experiments that activate the DR may have some merit here, in order to expose the patient to their feared panic sensations and to encourage them to challenge erroneous beliefs and give up their safety behaviours. Moreover, it would be really interesting for future research to investigate whether the CFI task can reduce the intensity and frequency of PAs by monitoring panic attack symptoms in the future, following CFI exposures.

According to Gallagher (2013) increasing patients’ sense of mastery and personal agency in their ability to cope with their symptoms, by correcting their maladaptive perceptions of bodily sensations has been shown to enhance recovery. Thus one proposed strategy to assist with increasing a patient’s sense of mastery, and sense of control is to educate them on the physiology of the DR and to encourage them to practice CFI regularly, as a way to reduce physiological and cognitive symptoms of anxiety. Based on our findings and the trained effects perceived in free divers, one may speculate that by practicing CFI on a regular basis, not only may one be able to reverse physiological symptoms of anxiety and panic but potentially prevent future PAs, something that warrants future investigation.
Chapter 7

QUALITATIVE EXPLORATION OF PANIC AND COLD FACIAL IMMERSION

7.1 RATIONALE FOR STUDY 2: QUALITATIVE INVESTIGATION

According to Gallagher et al. (2013), the most important factor for promoting recovery early in the treatment process involves correcting patients’ maladaptive perceptions of bodily sensations. This may be accentuated by patient psychoeducation on the diving response (DR) and its physiological adaptations and benefits. This powerful autonomic response can also be activated by the cold facial immersion (CFI) task or by other ways that may be regarded by the patient as more practical, in order to correct one’s maladaptive perceptions of bodily sensations or panic cognitions. Self-efficacy and anxiety sensitivity according to evidence may be the mechanisms of change of CBT for PD (Bouchard et al., 2007; Casey et al., 2005; Reilly et al., 2005; Shear et al., 2001; Smits et al., 2004; Gallagher et al., 2013).

Incorporating the DR in the existing treatments may complement already existing CBT treatments. The pronounced bradycardia experienced during the activation of the DR can help mediate catastrophic beliefs or misinterpretations. Hoffart et al. (2016) in his study found that catastrophic belief is a mediating factor contributing to either remission or persistence of PD. Decreasing catastrophic misinterpretations of bodily sensations using CBT can lead to overall changes in symptoms (Teachman et
al., 2010). According to Gallagher et al. (2013), the greatest changes occurring early in treatment was in anxiety sensitivity, while self-efficacy experienced greatest changes towards the end of treatment.

Evidence shows that CBT has the greatest effect on anxiety sensitivity which impacts changes in panic symptoms early in the treatment process when the focus of therapy revolves around providing psychoeducation, breathing retraining and cognitive restructuring which in turn impacts subsequent panic symptom changes (Gallagher et al., 2013). Effective and fast improvements have been observed in relation to patients’ fear of bodily sensations using CBT for PD (Gallagher et al., 2013).

Research has demonstrated CBT’s efficacy in decreasing anxiety sensitivity (Shear, Houck, Greeno, & Masters, 2001; Smits, Berry, Tart, & Powers, 2008; Gallagher et al., 2013) and further evidence reveals that anxiety sensitivity may be an important mechanism of change of CBT for PD that directly impacts other anxiety-related symptoms experienced (Reilly, Gill, Dattilio & Mc Cormick, 2005; Smits, Powers, Cho & Telch, 2004; Gallagher et al., 2013).

Delivering psychoeducation about anxiety-related bodily sensations, assisting patients develop a tolerance to these sensations, interoceptive and in vivo exposures exercises, and cognitive restructuring of catastrophic appraisals of anxiety-related bodily sensations, all part of CBT for PD, have been shown to decrease anxiety sensitivity in patients with PD (Barlow, 1988, 2002; Craske & Barlow, 2013; Gallagher et al., 2013).
7.2 AIM

This study aims to explore the current strategies used by clinical participants to manage anxiety and panic symptoms as well as understanding the key challenges experienced by individuals with PD in managing their symptoms. Furthermore, this study aims to explore the experience of CFI for clinical and control participants, as well as the challenges participants identify with using CFI and views around its utility as a treatment for managing anxiety and panic symptoms. Preferences of practical strategies to activate the DR are explored, and challenges discussed with the CFI task.

7.3 METHOD

7.3.1 Participants

A total of 30 participants, of whom 15 were males and 15 were females participated in this phase of Study 2. As per Study 2 reported in Chapter 6, 15 participants had a primary diagnosis of panic disorder with or without agoraphobia (PD) (DSM – 5), and 15 participants who did not meet criteria for PD or mental illness were recruited into the control group. The participants in the clinical group had an average age of 36.3 years (SD = 13.8), whilst the participants in the control group had an average age of 33.1 years (SD = 7.7). Both groups comprised 6 males and 9 females.
7.3.2 Materials

Appendix E includes the qualitative questionnaire that was used to interview participants from Group 1 and 2. Figure 25 provides an overview of the experimental procedure for this qualitative study.

Figure 25. Experimental procedure for the qualitative interviews for Group 1 (clinical) and Group 2 (control) participants.

7.3.3 Procedure

Two lists of questions were developed and agreed upon for the researcher to ask participants at Time 3 of Study 2. The first list of questions exploring challenges experienced and strategies used in managing anxiety and panic symptoms and thoughts. The second list of questions explored the participants’ experience of cold facial immersion and their views around its utility as an intervention to assist in managing anxiety/panic thoughts and symptoms. Participants of this study were recruited as part of Study 2 (see Chapter 6). Participants were required to complete a consent form, and consent to participate in an interview (see Appendix C for Plain Language Statement and Consent Form). Interviews were conducted face to face following the completion of the Time 3 task of Study 2 Phase 1. They were on
average 30 minutes in length. Clinical participants were asked both sets of questions, regarding their experience of their anxiety and panic symptoms, and their experience of the CFI task. For example, participants were asked, *What are the challenges you face in managing your anxiety/panic symptoms?* Participants in the control group were asked only the question in relation to their experience of the CFI task. For example, they were asked, *How would you describe your experience of cold facial immersion?* Demographic data such as age, gender, and current employment status was gathered as part of Study 2, Phase 1. The interviews were recorded and written verbatim and de-identified for data analysis.

### 7.3.4 Data Analysis

A thematic analysis of the 30 transcripts was undertaken. Initially, interview transcripts were grouped and analysed according to the type of questions (i.e., Anxiety/panic questions and CFI questions) and by group (clinical and control group). This resulted in 3 sets of data for analysis: Anxiety/panic related questions for the clinical group (15 transcripts), CFI experience questions for the clinical group (15 transcripts), and CFI experience questions for the clinical group control group (30 transcripts). For the analysis, an inductive approach was applied, where the identified categories and themes emerged from the data. Transcripts were read several times and a list of broad categories was developed and expanded as the analysis progressed. When allocating data to specific categories the “unit of meaning” was selected as the unit of coding (Dey 1993). Using this method, a unit of meaning is conveyed by content rather than form. As participants in qualitative interviews vary in the manner in which they express themselves, some succinctly and some more in-depth, consideration is not given to the number of words but rather to the meaning conveyed.
Once thematic categories were established from the initial exploratory research questions and coding was done using the QSR NVivo qualitative data analysis software package. The transcripts were initially coded to 23 broad categories identified in the data. Once the transcripts had been coded with the broad categories, text within categories was read and analysed to identify themes within categories. To establish sufficient reliability to proceed with the analysis and interpretation of the data, a second researcher familiar with the aims and objectives of the research reviewed the data, categories and themes within categories. This is known as the double coding method (Boyatzis, 1998). Discussions were held between the two researchers to reach agreement over the final categories and themes within categories.

For the questions relating to challenges experienced in managing panic/anxiety thoughts and symptoms for the clinical group refinement of an initial 13 categories (whereby categories were expanded, combined or renamed) resulted in five broad categories established. The five categories relating to challenges experienced in managing anxiety/panic included: cognitive disruption, disability burden, debilitating fear, debilitating symptoms, unhelpful thinking.

For the questions relating to strategies commonly used by clinical participants to manage anxiety/panic thoughts and symptoms for the clinical group refinement of an initial 10 categories (whereby categories were expanded, combined or renamed) resulted in three categories established. The three categories relating to strategies used in managing anxiety/panic included: Cognitive Strategies, Physical strategies, Mindfulness Strategies.
For the CFI experience questions for the clinical group refinement of an initial 16 categories (whereby categories were expanded, combined or renamed) resulted in 5 broad categories established. The five broad categories related to the clinical group’s CFI experience included: initial experience of CFI, post experience of CFI, practising CFI, perceived challenges with practicing CFI, and utility of CFI in assisting with panic and anxiety.

For the CFI experience questions for the control group refinement of an initial 14 categories (whereby categories were expanded, combined or renamed) resulted in 4 broad categories established. The four broad categories related to the control group’s CFI experience included: initial experience of CFI, positive experience after practicing CFI, perceived challenges with practicing CFI, and utility of CFI in assisting with panic and anxiety.

**7.4 RESULTS**

All 30 participants in Study 2 Phase 2 participated in the interviews result in 30 interview transcripts. The results of this study are presented in four parts. The first part reports the results of the thematic analysis of 15 transcripts relating to panic participant’s challenges in managing anxiety and panic thoughts and symptoms. The second part reports the results of the thematic analysis of 15 transcripts relating to strategies used by clinical participants to manage anxiety and panic thoughts and symptoms. The third section presents the results of the thematic analysis of 15 interview transcripts related to panic participant’s experience with the cold facial immersion (CFI) intervention. The fourth section reports the results of the thematic
analysis of 15 interview transcripts related to the control group’s experience of the CFI task.

7.4.1 Section 1. Challenges experienced in managing anxiety and panic thoughts and symptoms

The final categories and themes from the thematic analysis of the anxiety/panic qualitative questions administered to Group 1 appear in Table 17. The themes are described in further detail and individual quotes from participants are used for illustrative purposes. Participants identified a range of factors that challenge them in managing their anxiety/panic.
### Table 17.

**Themes and Categories in relation to Panic Cognitions and Symptoms for Group 1 (Clinical Participants)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Themes within categories</th>
<th>Participant Quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Disruption</td>
<td>Derealisation or Depersonalisation</td>
<td><em>You become detached, and everything becomes hazy.</em></td>
</tr>
<tr>
<td></td>
<td>Difficulty Thinking</td>
<td><em>I can’t think clearly.</em></td>
</tr>
<tr>
<td>Disability Burden</td>
<td>Avoidance</td>
<td><em>I try and avoid situations that will bring it on.</em></td>
</tr>
<tr>
<td></td>
<td>Escape Behaviour</td>
<td><em>I usually stay by myself to feel better with the sensations, or flee or run away.</em></td>
</tr>
<tr>
<td></td>
<td>Impact on daily functioning</td>
<td><em>With work, finding it hard to work, hard to stay in a job.</em></td>
</tr>
<tr>
<td>Anxiety and panic-related fear</td>
<td>Dying</td>
<td><em>I think I might die because my chest is moving up and down</em></td>
</tr>
<tr>
<td></td>
<td>Fainting</td>
<td><em>Well I’m scared of fainting</em></td>
</tr>
<tr>
<td></td>
<td>Loss of control</td>
<td>…symptoms come on and persist, I feel anxious and not in control</td>
</tr>
<tr>
<td></td>
<td>Uncertainty</td>
<td>The uncertainty and the fear is a challenge</td>
</tr>
<tr>
<td>Panic Cognitions</td>
<td>Predictive &amp; Catastrophic Thinking</td>
<td><em>….think about things which might go wrong</em></td>
</tr>
<tr>
<td></td>
<td>Racing Thoughts</td>
<td><em>when the onset of the panic attack is occurring, I usually the mind is racing</em></td>
</tr>
<tr>
<td></td>
<td>Worrying</td>
<td><em>continual probably worrisome thought process that leads eventually to a panic attack</em></td>
</tr>
<tr>
<td>Physiological Symptoms</td>
<td>Cardiorespiratory Symptoms</td>
<td><em>Struggling to breathe, I don’t realise that I’m not breathing at all.</em></td>
</tr>
<tr>
<td></td>
<td>Vestibular Symptoms</td>
<td><em>If I am having a panic attack it’s usually I get hot flushes.</em></td>
</tr>
</tbody>
</table>
Chapter 7

Exploration of Panic and Cold Facial Immersion

7.4.1.1 Cognitive Disruption experienced during anxiety and panic

Derealisation or Depersonalisation

When asked what challenges participants experience in managing anxiety or panic symptoms many discussed feeling a sense of being so overwhelmed by their symptoms that they lose touch with reality:

...you lose a sense of reality...

You become very detached.

Difficulty Thinking

When asked what challenges participants experience in managing anxiety or panic thoughts many discussed difficulty in ordering their thoughts:

...anxiety and panic thoughts are entangled, can’t separate them from one another, makes it more difficult...

I can’t think clearly.

7.4.1.2 Disability Burden of panic and anxiety

Avoidance Behaviour

When asked what challenges participants experience in managing anxiety or panic thoughts many discussed having to avoid situations that might trigger anxiety or panic:
On a plane for example, I do not travel if I do not get an aisle seat. There is no way that I will be able to travel on a plane if I have to sit between people or you know there’s no way out.

.. in a back seat of a car I will never sit in between and if there’s a crowded train I will never get on it.

Escape Behaviour

When asked what challenges participants experience in managing anxiety or panic thoughts many discussed feeling a strong need to escape situations:

I get a strong feeling or need to escape.

Disruption to daily functioning

When asked what challenges participants experience in managing anxiety or panic thoughts many how their symptoms and thoughts impact their ability to engage in everyday life:

With work, finding it hard to find work, hard to stay in a job

And if I need to do something then I will spend a lot of time preparing and informing myself.

7.4.1.3 Anxiety and panic-related fear

Fear of Dying

Catastrophic thinking and in particular a fear of dying was evident in many of the clinical participants:
Difficulty with fear of death, I think I might die because chest is moving up and down.

Initially it was a huge challenge. I didn’t understand what was happening. So you really believe those symptoms that you’re going to die; that you’re going to have a stroke that you need to call an ambulance...

Fear of Fainting

A fear of fainting was also discussed by a couple of clinical participants:

well I’m scared of fainting

I have thoughts around feeling faint, thinking that I would pass out

Loss of control

A sense of losing control or not being in control was a challenge that many clinical participants discussed in relation to managing both symptoms and thoughts related to panic and anxiety:

Difficult to control thoughts in beginning try to stay calm symptoms come on and persist I feel anxious and not in control

I feel something is wrong with me, I can’t control the symptoms because I’m overwhelmed by them.

Fear of uncertainty

A sense of not knowing what is happening was also discussed as a challenge in relation to managing anxiety and panic:

Being unsure of what is happening
...how long is it going to last? Is it going to be a lengthy one? Is it going to go fast? That uncertainty and the fear is a challenge

7.4.1.4 Anxiety and panic cognitions

Predictive and catastrophic thinking

The majority of clinical participants reported a preoccupation with predictive or catastrophic thoughts that contributed to their challenge in managing anxiety and panic:

...thinking about things which might go wrong

...trying to predict what can happen you know, or is it happening right now

I think I might die because my chest is moving up and down.

Racing thoughts

Trying to manage racing thoughts associated with anxiety and panic was described as a significant challenge for clinical participants:

When the onset of the panic attack is occurring, usually the mind is racing..

Thoughts, yeah thoughts can race.... I can leap around from some different subject matters randomly, they’re not linked at all.

Worrying

General worrying was also discussed by clinical participants as a contributor to the challenge of managing panic and anxiety thoughts and symptoms:

..continual probably worrisome thought process that leads eventually to a panic attack..
I worry about things which might go wrong

7.4.1.5 Physiological Symptoms

Respiratory Symptoms

Coping with respiratory symptoms associated with anxiety and panic were described as major challenges for clinical participants:

Struggling to breathe, I don’t realise that I’m not breathing at all

Challenges are more breathing, like I know that... When I’m anxious I don’t breathe well.

Vestibular Symptoms

Participants also described difficulties in coping with the following vestibular symptoms:

Shakiness that I feel that’s challenging, feeling somewhat disorientated.

The most challenging thing and my trembling...and of course the trembling gets to the point that everyone notices, that disturbs me a lot
Section 2. Strategies used to manage anxiety and panic thoughts and symptoms

The final categories and themes from the thematic analysis relating to strategies used by clinical participants to manage anxiety/panic thoughts and symptoms appear in Table 18. The themes are described in further detail and individual quotes from participants are used for illustrative purposes. Participants identified a range of strategies they use to assist them in managing their anxiety/panic.
Table 18.

Themes and Categories relating to panic management strategies for Group 1

(Clinical participants)

<table>
<thead>
<tr>
<th>Category</th>
<th>Themes within categories</th>
<th>Participant Quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Strategies</td>
<td>Thought Stopping</td>
<td>Stop yourself from generating negative….. panicky thoughts</td>
</tr>
<tr>
<td></td>
<td>Self talk and Reassurance</td>
<td>I started to tell myself, I started to self-talk myself out go it.</td>
</tr>
<tr>
<td></td>
<td>Psychoeducation</td>
<td>I did a lot of reading, and that helped me understand.</td>
</tr>
<tr>
<td></td>
<td>Distraction and Refocus</td>
<td>Yeah I will find distractions, things that I can really concentrate on, like a singular thing.</td>
</tr>
<tr>
<td>Physical Strategies</td>
<td>Breathing techniques</td>
<td>I would concentrate on the breathing which is a good distraction so it helps the anxiety to pass</td>
</tr>
<tr>
<td></td>
<td>Physical activity</td>
<td>I try to do a bit of stretching….because I get a lot of muscle tension.</td>
</tr>
<tr>
<td>Mindfulness Strategies</td>
<td>Mindfulness and Acceptance techniques</td>
<td>I would just relax and take a breath, and before this I would just let the anxiety do its thing, let the panic attack happen</td>
</tr>
<tr>
<td></td>
<td>Meditation</td>
<td>I use prayer meditation</td>
</tr>
</tbody>
</table>
7.4.2.1 Cognitive Strategies used to manage anxiety and panic

Thought Stopping

A common strategy discussed by clinical participants was trying to put a stop to thoughts that were contributing to their panic and anxiety:

...stop yourself from thinking

Stop yourself from generating negative..... panicky thoughts

Self-talk and Reassurance

When asked what strategies they employed to assist them in managing panic and anxiety symptoms, many discussed using self-talk and reassurance:

..... you just tell yourself it will pass. And that’s what you keep telling yourself. You’re not going to die, you’re not having a stroke.

Yeah, you almost have to tell yourself it isn’t real it isn’t happening especially when you’re in that really heightened state of panic.

Psychoeducation

Among the strategies discussed, clinical participants mentioned educating themselves on their conditions and learning about themselves as helpful in managing their panic and anxiety:

So the way I did, because my personality is that type, I started to research and investigate it myself. So I did a lot of reading, and that helped me understand.
Distraction and Refocus

Many clinical participants described the use of distraction techniques and trying to refocus their thoughts:

I would concentrate on the breathing which is a good distraction so it helps the anxiety to pass.

trying to focus more on thoughts on one single thing.

refocusing the thoughts correctly

Also, and I try not to do this too much, but I do find other things to do as a form of distraction. Such as playing an instrument, or reading a book, messing around on the computer.

7.4.2.2 Physical Strategies

Breathing Techniques

When asked what challenges participants experience in managing anxiety or panic symptoms many discussed feeling a sense of being so overwhelmed by their symptoms that they lose touch with reality:

Breathing... yes I try but it doesn’t help me I try whenever I feel that I might get a panic attack....I do breathing exercises before... but I’m not too sure whether that works to be honest

I have also practiced breathing techniques, taking deep breaths. With long pauses. And then you try and do those deep breaths....

I’ve tried mindfulness and relaxation, and controlled breathing, but it’s not as effective as I would like it to be
Physical Activity

Another strategy discussed by clinical participants, was exercising and trying to keep physically active:

*I feel like... that I... needed to go for a run*

*I’ve been trying to incorporate some form of exercise as well but I have very limited energy for each day... I try to do a bit of stretching as well, because I get a lot of muscle tension.*

7.4.2.3 Mindfulness Strategies

Mindfulness and Acceptance

Using the practices of mindfulness and acceptance were discussed by many clinical participants as a strategy that they employ to assist in the management of anxiety and panic symptoms:

*I would just relax and take a breath, and before this I would just let the anxiety do its thing, let the panic attack happen*

*I stay with the sensations or my thoughts and just notice them. Sometimes it may be helpful to sit with the emotions and thoughts and just watch them.*

*Mindfulness, that’s something that when I do think of it, I then focus on things, I focus on things that I smell or what I’m looking at…*

*Mindfulness, controlled breathing, relaxation, challenging and distracting myself, re-adjusting my thinking process from obsessing about health concerns*
Chapter 7. Exploration of Panic and Cold Facial Immersion

Meditation

Whilst mindfulness was most commonly discussed, some clinical participants specifically identified meditation as a strategy to manage anxiety and panic symptoms:

*I use prayer meditation*

*Doing those sorts of things it’s a bit of like meditation where, you, kind of, focussing on one area, and that, I found that can help, a lot.*

7.4.3 Section 3. Experience with cold facial immersion task for clinical participants

The final categories and themes from the thematic analysis relating to the experience of cold facial immersion and views around its utility in helping manage anxiety/panic for clinical participants appear in Table 19. The themes are described in further detail and individual quotes from participants are used for illustrative purposes. Participants described their experience and perceptions of the cold facial immersion task and its utility as an intervention.
Table 19.

**Themes and Categories regarding Participants Experiences of the Cold Facial Immersion Task for Group 1**

<table>
<thead>
<tr>
<th>Category</th>
<th>Themes within categories</th>
<th>Participant Quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial experience with CFI</strong></td>
<td>Relaxed state</td>
<td>I...felt relaxed while my face was immersed</td>
</tr>
<tr>
<td></td>
<td>Calm effect</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Physical Discomfort</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anticipatory Anxiety</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I felt, a rush of calmness while ...my face was in there</td>
<td></td>
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<tr>
<td></td>
<td>I felt sinus pain... above the bridge of the nose... it was just like pressure</td>
<td></td>
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<tr>
<td></td>
<td>I felt scared to begin with but knew things were under control</td>
<td></td>
</tr>
<tr>
<td><strong>Experience post CFI</strong></td>
<td>Relaxed state</td>
<td>I was surprisingly really relaxed</td>
</tr>
<tr>
<td></td>
<td>Calming effect</td>
<td>My thoughts went away felt frozen at the moment. Really present.</td>
</tr>
<tr>
<td></td>
<td>Mindful state</td>
<td>...easier to focus on the here and now</td>
</tr>
<tr>
<td></td>
<td>Reduced panic symptoms and cognitions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I didn’t have the thoughts, sensations and symptoms of anxiety that I usually have</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Confidence and Empowerment</td>
<td>Once it’s done you get this feeling of accomplishment.</td>
</tr>
<tr>
<td><strong>Practicing CFI</strong></td>
<td>Motivation to practice CFI</td>
<td>I want to practice CFI, as hopefully it will help</td>
</tr>
<tr>
<td></td>
<td>Predicted regularity of practice</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Practice during panic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very likely, to practice it in a panic attack, because found it helpful</td>
<td></td>
</tr>
<tr>
<td><strong>Perceived challenges with practicing CFI</strong></td>
<td>Time challenges</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Physical challenges</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Accessibility and convenience</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Social Acceptance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I...it’s more finding the time... cos I’m pretty busy</td>
<td></td>
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<tr>
<td></td>
<td>Only challenge is lasting 30 seconds, and increasing the capacity for breath-hold.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>the only challenge I see is access to the cold water when out, it’s kind of you know weird to do it in public</td>
<td></td>
</tr>
<tr>
<td><strong>Utility of CFI in assisting panic/anxiety</strong></td>
<td>Simplicity and practicality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reducing panic symptoms and thoughts</td>
<td>I think it’s great... something so simple, that can calm you.</td>
</tr>
<tr>
<td></td>
<td>Effectiveness as an intervention</td>
<td>It reduces panic symptoms and negative thoughts...very helpful</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I think it would be beneficial, it would be effective for most people</td>
</tr>
</tbody>
</table>
7.4.3.1 Initial experience with the cold facial immersion (CFI) task

Relaxed state

Many clinical participants described a general state of relaxation in the initial stages of the cold facial immersion task:

... felt comfortable after 10 seconds. Felt relaxed by the end of it. I was stressed that I won’t last 30 seconds but I got through it.
I...actually felt relaxed while my face was immersed
... when I put my face into the cold water I just thought like the temperature just brought my heart rate down

Calm effect

When describing their initial experience clinical participants also discussed feeling calm as a result of the cold facial immersion task:

I felt, a rush of calmness while my face was in there
... when I realized how calming it all was I allowed, myself to experience that calmness and embrace it. So when I came up, I was still in that, calm level.

Physical Discomfort

Although some clinical participants described feelings of relaxation and calm, it was evident that some participants’ experience of the cold facial immersion task involved some physical discomfort:

I felt a bit dizzy...or not dizzy but disoriented ...from the cold water
... apart from getting a bit of pain in the sinus area because the water was cold...but turned out I had some sort of cold coming on

**Anticipatory Anxiety**

Some participants talked about a general feeling of uncertainty and feeling fearful and nervous in the lead up and/or at the beginning of the cold facial immersion task:

*I felt scared to begin with but knew things were under control.*

*Initially I was petrified.*

*Yeah. I was more anxious before*

Feeling anxious before the CO₂ challenge was an experience described by some of the participants:

*I didn’t have an immediate... anxiety, until...shortly after once everything went back to room temperature, right before I inhaled the mixture, there was, I started to feel some, worry thoughts I think that was more to do with the fact that I was about to inhale; knowing what was coming next; or what I was supposed to do next*

A lack of belief in being able to hold their breath for the duration of the CFI task also raised some concerns among some of the participants:
... I didn’t know what to expect. I didn’t think I would be able to hold my breath for 30 seconds. The shock of the water, didn’t think I would last 30 seconds.

I was actually worrying about... if I could actually hold my breath long enough and not spoil the experiment.

### 7.4.3.2 Experience after completing with the cold facial immersion (CFI) task

#### Relaxed state after CFI

Following completion of the CFI task, many of the clinical participants described a state of relaxation:

> Once I came out of the water, felt relaxed. Felt good that I lasted 30 seconds.

And relaxed after.

> I was quite surprised I could hold my breath for that long, and really was quite relaxing to be honest.

> I was surprisingly really relaxed.

Some participants also described the experience of a lowered, more relaxed heart rate:

> I noticed the relaxing heart rate, I felt mellow, relaxed, and wasn’t as fearful of taking a breath of the CO\(_2\). So it was easier following the CFI
Calming effect

When asked how they felt following the CFI task, many clinical participants also reported feeling a state of calm:

*I did not feel too tense... after I did the cold water immersion. If you ask me about you know how tense I felt I think I felt relatively calm... after immersion*

*There was no surprises, there was no funny sensations through my body or my mind... [I felt] perfectly calm you know...*

*I certainly felt calm from the cold water.*

Mindful State

Some clinical participants also reported a state of mindfulness following completion of the CFI task:

*Thoughts went away felt frozen at the moment. Really present.*

*...easier to focus on the here and now*

*The CFI distracts everything, distracts my thinking, because I was concentrating on getting to the 30 seconds and the breath-holding*

Reduced panic symptoms and cognitions

Many of the clinical participants described having reduced or the absence of panic thoughts and symptoms following completion of the CFI task:

*It reduced my panic yes because I felt it reduced anxiety, because before I had a lot of high anxiety which is anticipatory*
The cold water got rid of fear or anxiety or panic thoughts. Felt no anxiety or panic.

I didn’t have the thoughts, sensations and symptoms of anxiety that I usually have

I didn’t have any worrying thoughts at all, I think because I was so surprised how pleasant the experience

Some participants went beyond describing an absence of panic cognitions and symptoms to reporting positive and optimistic thinking:

Following the CFI, thoughts were positive, I have more of a positive mindset, because it was relaxing it cleared my mind and thoughts

My optimistic thinking improved...

Confidence and Empowerment

Clinical participants described a sense of confidence and accomplishment at being able to complete the CFI task:

So it was easier following the CFI. I felt empowered about managing my symptoms, I feel more confident now. The CFI distracts everything, distracts my thinking because if I get through something difficult I feel more confident, and the next time I don’t think about it as much

...once it’s done you get this feeling of accomplishment.
7.4.3.3 Practicing CFI

Motivation to practice CFI

Participants were asked about the likelihood they would practice CFI and more specifically how motivated they would be in using CFI as a strategy to assist with management of panic and anxiety thoughts and symptoms. Many described it being a good strategy and feeling motivated to practice it if they needed:

*It would definitely help me out. I wouldn’t be scared at home alone. It’s a good strategy, it teaches you to relax and calm down. As you calm down so quickly, it’s very effective.*

*I see it as an excellent strategy to reduce symptoms. I could keep calm, walk to bathroom, put cold water in face when having a panic attack, this would relax me.*

*I want to practice CFI, as hopefully it will help, very hopeful, it did help in the lab but that was in a controlled setting. Should do it when panic sensations coming on.*

*Hopeful as I wasn’t fearful when I was practicing the cold facial immersion.*

7.4.3.4 Perceived challenges with practicing CFI

Time challenges

Some clinical participants identified that finding the time to set up and practice CFI as a challenge:

*Yeah it’s more finding the time… cos I’m pretty busy.*
Partly the time to set it up but also the fact that, I would be constantly distracted. Due to the fact that I have young children. It’ll be a different story when they’re at school.

Physical challenges

Challenges with breath-holding and water temperature were among some of the physical challenges identified by clinical participants:

... taking a deep breath, and if not in control, if I was to take a deep breath, it would help, as it would calm my symptoms so I think it would be a win-win.

... lasting 30 seconds, and increasing the capacity for breath-hold. I think it would help me particularly with my anxiety and panic, as I hyperventilate and need to take deeper breaths.

Accessibility and convenience

Clinical participants also discussed convenience of practicing CFI in certain situations, and being able to access water as potential challenges to practicing CFI:

Only challenge is finding ice or access to cold water when out

Well obviously access to water, a container where you can... submerge your face, that’s obviously not always available, and you know something that you need to organise when it happens...

I’m in a truck all day so... it’s not like I can find the nearest bucket to fill water up... that’s going to be a challenge, it’ll be hard if I can’t use it if I’m at work or anywhere else.
Social Acceptance

Challenges with practicing CFI in public places or whilst out were also identified as potential barriers to practicing CFI:

*I don’t see any challenges, other than being in public in front of others. That’s the only challenge as I would feel embarrassed sometimes, depending on where I am and who I am with.*

*You are going to look silly if you’ve got all wet hair coming out of the [water].*

7.4.3.5 Predicted regularity of practice

Following on from motivation to practice CFI, participants were asked how regularly they could see themselves using CFI. Many of them indicated it would be a practice they would use regularly:

*…whatever I find effective, I use on a regular basis*

*…if I found that it was effective you know of course I would, I would really do anything to try and help out you know the onset of an anxiety or panic attack, because it’s not a nice experience to go through*

Some participants also commented on the likelihood that they would use it whilst having a panic attack:

*Very likely, to practice it in a panic attack, because found it helpful, I don’t see any challenges with it. It’s a strategy that I have to do more often*

*…it’s…difficult when I’m …out but if I’m at home…I can like just wash my face with some cold water in the sink*
7.4.3.6 Utility of CFI in assisting panic/anxiety

Simplicity and practicality

When considering the usefulness of cold facial immersion as a strategy for managing anxiety and panic some clinical participants commented on the simplicity and practicality of CFI:

I've gone to a psychologist...to help me with my panic attacks...the programs are almost...impossible to follow. By using this which is a very simple technique ... I think I would feel much better

Depending on results I think...it would be the most....easiest technique for someone who has...if you want to treat panic disorders it requires.. breathing exercises, you know thrice a day, then muscle exercise twice a day... you know you have to follow it very strictly...so it is difficult.... this technique will be very easy, you can do that, in the shower...

I can see it rolling it out as an intervention, each time you have anxiety putting your face in cold water as this is a very easy to use method and practical.

Some clinical participants also discussed the utility of using CFI to reduce panic symptoms and thoughts during panic attacks:

It reduces panic symptoms and negative thoughts, I think it would be very helpful

I want to practice CFI, as hopefully it will help, very hopeful, it did help in the lab but that was in a controlled setting. Should do it when panic sensations coming on.

Well it can help me relax and forget about the anxiety.
Effectiveness as an intervention

When considering its long term use, some participants considered CFI to be a potentially useful intervention for managing panic and anxiety thoughts and symptoms:

“It would definitely help me out. I wouldn’t be scared at home alone. It’s a good strategy, it teaches you to relax and calm down. As you calm down so quickly, it’s very effective. I see it as an excellent strategy to reduce symptoms. I could keep calm, walk to bathroom, put cold water in face when having a panic attack, this would relax me.

From what I’ve learnt I think it would be very beneficial. So I even think that if I ever start to get into a state of panic I might actually a bucket of water and just throw my face into it. I think that would be very beneficial. Definitely.

... I would see it, well in the future in would be a very good intervention, like a very good technique to help people... who have anxiety and panic disorders.
7.4.4 Section 4. Experience with cold facial immersion task for control participants

The final categories and themes from the thematic analysis relating to the experience of cold facial immersion and views around its utility in helping manage anxiety/panic for control participants appear in Table 20. The themes are described in further detail and individual quotes from participants are used for illustrative purposes. Participants identified a range of strategies they use to assist them in managing their anxiety/panic.
Table 20.

**Themes and Categories regarding Participants Experiences of the Cold Facial Immersion Task for Group 2**

<table>
<thead>
<tr>
<th>Category</th>
<th>Themes within categories</th>
<th>Participant Quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial experience of CFI</td>
<td>Mindful calming effect</td>
<td><em>I felt the coldness calmed me down</em></td>
</tr>
<tr>
<td></td>
<td>Relaxed state</td>
<td><em>Relaxing, could feel tension in facial muscles reduced</em></td>
</tr>
<tr>
<td></td>
<td>Reduced Heart rate</td>
<td><em>I felt the heart rate was going down</em></td>
</tr>
<tr>
<td></td>
<td>Anticipatory Anxiety</td>
<td><em>Yeah I was a bit nervous holding my breath...</em></td>
</tr>
<tr>
<td></td>
<td>Discomfort with cold water</td>
<td><em>... it was difficult to hold my breath for that long, 30 seconds</em></td>
</tr>
<tr>
<td>Positive experience after practicing CFI</td>
<td>State of Mindfulness</td>
<td><em>I think they [thoughts] were really reduced on the moment</em></td>
</tr>
<tr>
<td></td>
<td>Relaxed state and reduced heart rate</td>
<td><em>straight away I could definitely feel my heart..beating slower</em></td>
</tr>
<tr>
<td></td>
<td>Reduced anxiety symptoms and thoughts</td>
<td><em>Could feel anxiety go down...</em></td>
</tr>
<tr>
<td></td>
<td>Sense of confidence and accomplishment</td>
<td><em>I felt like I had more self confidence</em></td>
</tr>
<tr>
<td>Perceived challenges with practicing CFI</td>
<td>Accessibility and convenience</td>
<td><em>Having access to cold water if I'm outside somewhere.</em></td>
</tr>
<tr>
<td></td>
<td>Social Acceptance</td>
<td><em>...it’s kind of you know weird to do it in public some people don’t feel as comfortable with their face under water</em></td>
</tr>
<tr>
<td></td>
<td>Physical discomfort with water</td>
<td></td>
</tr>
<tr>
<td>Utility of CFI in assisting panic/anxiety</td>
<td>Effective stress and anxiety relief</td>
<td><em>Well it can help me relax and forget about the anxiety</em></td>
</tr>
<tr>
<td></td>
<td>Induce mindfulness and relaxation</td>
<td><em>I find being in cold water relaxing</em></td>
</tr>
<tr>
<td></td>
<td>Simplicity and practicality</td>
<td><em>It’s easy and practical to use...people can practice this quite easily</em></td>
</tr>
<tr>
<td></td>
<td>Useful for people that suffer anxiety</td>
<td><em>I would also recommend it to people who are going towards panic attacks</em></td>
</tr>
<tr>
<td></td>
<td>Likelihood of practicing CFI</td>
<td><em>I would recommend it to friends and family. I would practice it more often</em></td>
</tr>
</tbody>
</table>
7.4.4.1 Initial experience of CFI

Mindful calming effect

Many control participants described a mindful and calm state in the initial stages of the cold facial immersion task:

*It was refreshing*

*It was really good, it was calming in the sense that, yeah, you just couldn’t hear anything and it was just everything was blocked out for a bit.*

*.. the calming effect within one or two seconds I could feel myself slowing down.*

Relaxed state

Many control participants also described feeling relaxed during the initial stage of the CFI task:

*Relaxing, could feel tension in facial muscles reduced,*

*Relaxing..*

*...when I took my head out I actually felt quite refreshed and felt quite nice actually*

Reduced Heart rate

Some of the control participants also reported feeling a reduction in their heart rate in the initial stages of the CFI task:

*Well… when I put my face into the cold water I just thought like the temperature just brought my heart rate down*

*I felt the heart rate was going down*
Anticipatory Anxiety

Some control participants described experiencing anticipatory anxiety before and in the initial stages of the CFI task, particularly with regard to being able to hold their breath for 30 seconds:

Yeah I was a bit nervous holding my breath...

I guess before the face immersion, I probably had a little bit of anxiety, because I even asked “Do I have to hold my breath for 30 seconds?” Because I questioned it, and I thought I don’t know if I can…like I don’t know I’ve never tried this before, I haven’t been underwater before, like scuba diving and I’m uncomfortable with water...

Discomfort with cold water

Furthermore some control participants reported some level of discomfort in the initial stages of the CFI task:

...I felt a little hot after a few seconds

I felt cold towards the end of 30 seconds,

I felt dizzy and jittery

7.4.4.2 Positive experience after practicing CFI

State of Mindfulness

Many control participants discussed feeling a state of mindfulness following the completion of the CFI task:

..calm...similar to like doing, like meditating or yoga or something, just calming...
I guess it just completely clears your mind, I wasn’t really thinking of anything..

Oh yeah I think they [thoughts] were really reduced on the moment

Relaxed state and reduced heart rate

Following completion of the CFI task, many of the control participants described a state of relaxation:

The feeling that I had afterwards it was like...when you go for a swim in the ocean, and then afterwards... you kind of feel relief and refreshed...

I feel like straight after [CFI] it was just such a relaxing sensation, I kind of wanted to stay like that but obviously it didn’t last that long...

Reduced anxiety symptoms and thoughts

When asked how they felt following the CFI task, many control participants also reported experiencing reduced anxiety symptoms and thoughts:

I was a bit nervous going into it, and then like, I don’t really remember what I was thinking...

I was just kind of like waiting for what was gonna happen but I just felt calm and just kind of relieved...

My optimistic thinking improved

Sense of confidence and accomplishment

Some control participants also reported feeling a sense of confidence and accomplishment upon completing the CFI task:
And I could say it was.. I felt like I had more self confidence

I had more self confidence

I was surprised I could hold my breath for thirty seconds without really having trained for it.

7.4.4.3 Perceived challenges with practicing CFI

Accessibility and convenience

Some control participants identified that accessibility to water and convenience were some of the potential challenges with practicing CFI:

I was thinking maybe time.... if I had to get ready to go for work, it's not ideal time, ....but maybe like, I don't know like... as soon as you wake up, it would be good...

Access to the bucket or cold water that you can actually immerse your face in.

Another possible challenge would be that when I’m actually in a situation where I’m experiencing panic or anxiety, I think it would be difficult to prepare all the things needed for CFI, for example the pale and cold water.

Social Acceptance

Some control participants identified that accessibility to water and convenience were some of the potential challenges with practicing CFI:

I don’t know...in your house it’s more practical, there isn’t no other persons...I guess with me personally embarrassment in public
if I was out no, and for me I think when I’m feeling anxious it’s more so when I’m out, you know more like social anxiety. So in that sense probably not so practical.

Physical discomfort with water

Some control participants also mentioned physical discomfort with water as a potential barrier for practicing CFI:

You know, some people don’t feel as comfortable with their face under water. I taught a ‘learn to swim’ program and you know, half of the system is just teaching people to keep their face in the water. So that might be a difficulty. But for your every day average person who doesn’t mind it – I think it will be fine.

7.4.4.4 Utility of CFI in assisting panic/anxiety

Effective stress and anxiety relief

When asked about the usefulness of CFI in assisting in the management of anxiety and panic, many control participants identified discussed its use as a form of stress and anxiety relief:

If I ever felt that I was anxious I think it would help it..because it helps relax. So it would definitely help relax the situation.

It could really assist me if I have anxiety as I felt refreshed and this may help with stress and anxiety.

I think it would be a great way to help control many of the physical symptoms of anxiety, as the CFI has a very calming effect.
Induce mindfulness and relaxation

Another common benefit identified by control participants as adding to the effectiveness of CFI in assisting the management of anxiety and panic was that it induced mindfulness and relaxation from their experience:

"It's also very good distraction. It's a very mindful experience I can see this calming me and my anxiety and stress and in terms of thinking as well

It's like...going swimming in the ocean, it's like...almost like refreshing...

and like you're putting something in the past and then kind of looking at something in a different way. I don't know how to explain that...

It will definitely lower the heart rate, bringing down anxiety, it will be beneficial definitely. Blood flow to the head is relaxing following the cold facial immersion, that will definitely help me relax. With panic and anxiety thoughts, I think it will help because of the shock to the system, and because of the thoughts stopping

Simplicity and practicality

Many control participants also emphasised the simplicity and ease with which you can practice CFI as another benefit in its effectiveness to assist individuals in managing anxiety and panic:

"I think a combination with other things, even if you were to do this regularly at home, as such, I think you know if you’re you know a place where you can’t really you know excuse yourself for a few minutes to go and do that, then you could use other techniques"
This would impact me in a positive way. I would let other people know about this technique because it's easy and practical to use, and people can practice this quite easily.

Useful for people that suffer anxiety

Many control participants discussed CFI specifically in terms of its usefulness in assisting individuals that suffer from anxiety:

Yeah pretty positive like it seems to be helping...I think it’s positive, I think it would be helpful and not many people would have probably considered something like this so... like I haven’t considered it until the start of the research I suppose

It’d be a positive impact and I would then also recommend it to other people.

I guess if it’s been proven to work, then the fact that can also lend support to, when you’re describing it to the person to give them confidence, well it’s been tested and it actually works

Likelihood of practicing CFI

When asked about whether participants were likely to practice CFI, many participants indicated it would be something they would consider practicing:

It could really assist me if I have anxiety as I felt refreshed and this may help with stress and anxiety. It's also very good distraction. It's a very mindful experience I can see this calming me and my anxiety and stress and in terms of thinking as well

If it had more of an empirical basis, I would be more likely to practice, and it will have a positive impact
7.5 DISCUSSION

The aims of the current study were to identify the current challenges which clinical participants have managing their panic and anxiety symptoms and thoughts, as well as the participants’ experience of cold facial immersion (CFI) and their views around its utility as an intervention to assist in managing anxiety/panic thoughts and symptoms. The results from this qualitative study proved to be a rich source of data, enabling the illumination of some valuable information. They will be discussed in two parts, firstly the current challenges will be discussed and then the experience and application of the CFI task.

7.5.1 Challenges with the management of anxiety and panic thoughts and symptoms

The key factors identified related to anxiety/panic management of thoughts and symptoms included: cognitive disruption, disability burden, anxiety and panic-related fear and panic cognitions. Cognitive disruption entailed challenges like derealisation and depersonalisation themes, and difficulty thinking and concentrating. There is an obvious manifestation of cognitive disruption in both state and clinical anxiety (Vytal et al., 2013). Cognitive functions such as spatial working memory (Lavric et al., 2003, Shackman et al., 2006) and particularly verbal working memory respectively may be disrupted by anxious apprehension and anxious arousal. Verbal working memory processes may share more neural circuitry with anxious apprehension and anxious arousal hence accounting for the exaggerated disruption (Vytal et al., 2013). The cognitive disruption experienced by Panic Disorder (PD) sufferers characterised by difficulty concentrating and feeling easily distracted, has
been undoubtedly linked to their disability burden as it can negatively impact their performance at work and interpersonal relationships (Vytal et al., 2013).

Disability burden was a key factor found to be a challenge in managing anxiety symptoms and thoughts by the clinical participants. The themes identified comprised avoidance/escape behaviours and impact on daily functioning which depict the magnitude of one’s perceived experience of feeling debilitated. PD is among the anxiety disorders that can have a significant impact on peoples’ lives. Our findings correspond with previous research that reported that PD accounted for high levels of social, marital, occupational and physical disability (Klerman et al., 1991; Ettigi et al., 1997) and in the primary health-care and community settings, PD is regarded as one of the most costly mental health conditions (Meuret et al., 2017; Kessler et al., 2005), being potentially more of a disability burden than even the severe mental disorders (Baxter, Vos, Scott, Ferrai & Whiteford, 2010; Kessler, et al., 2006, Kennedy & Schwabb, 1997).

Avoidance and escape behaviours which were identified as themes associated to the disability burden may occur in response to perceived threat and anxiety, and in turn, may drive to maintain the perceived threat and anxious beliefs (Funuyama et al., 2013). According to Forsyth, Barrios and Acheson, (2007) following several trials of CO₂ inhalations individuals high in experiential avoidance, present with more panic symptoms, panic cognitions, fear, and loss of control than their less avoidant counterparts.
Salkovskis, Clark and Hackmann, (1991) proposed that exposure therapy although effective in the treatment of phobias can be compromised by the implementation of in-situation safety behaviours, and/or subtle avoidance strategies aimed to prevent the perceived threat or feared catastrophe while remaining in the feared situation. Such safety behaviours and avoidance strategies that are applied in phobic situations by the anxiety sufferer prevents him/her from experiencing an unambiguous disconfirmation of their erroneous beliefs, regarding feared catastrophes (Salkovskis et al., 1991; Salkovskis, Clark & Gelder, 1996).

Impact on daily functioning was notable as an important theme, playing a role in contributing to the disability burden of clinical participants in Study 2. PD is often considered to have a chronic course which has been associated with having significant life impairment, including substance abuse, and increased likelihood of suicide attempts, unemployment, frequent absenteeism, early retirement and regular use of health care services (Ettigi et al., 1997). This impact on daily functioning caused by the chronic nature of the symptoms, the avoidance and escape behaviours and the debilitating physiological and cognitive symptoms reported generally by PD patients impact pose a significant challenge in managing anxiety symptoms, and panic and anxiety thoughts.

According to Cosci (2012) promoting recovery early in the treatment process is important, given that PD often involves a staging process, implicating that the disorder often gradually worsens over time if left untreated. Support for the staging model of PD and agoraphobia has been implicated by its utility to recognise PD early enough to be able to treat it successfully (Fava et al., 1999; McGorry 2007; Mc Gorry
et al., 2007). The model may also be able to assist with the development of therapeutic strategies for patients that are treatment resistant (Cosci, 2012).

Anxiety and panic-related fear was another key area identified which encompassed the following themes: fears of dying, fainting, losing control and uncertainty. All these themes pose significant challenges given that fear is very much accentuated in the abovementioned perceived threats. These fears may be quite common in anxiety provoking situations in anxiety sufferers, however in PD sufferers they are more vast and scary given that individuals fear their own bodily symptoms, losing control and uncertainty. These are more exaggerated in the PD group given that PD is characterised by recurrent and spontaneous panic attacks (PAs). Clinical participants reported fears and exaggerated anxiety to the unlikely prospect that they may faint, pass out, die, or have a heart attack.

Loss of control and fear of uncertainty were a challenge that many clinical participants discussed in relation to managing both symptoms and thoughts related to panic and anxiety. Particularly participants described having difficulty controlling their thoughts and anxiety/panic, as their symptoms are often exaggerated due to disproportionate fear experienced and the uncertainty of not knowing when the PA will cease. Participants reported having difficulty with the uncertainty, i.e., whether they will be able to cope, how long the PA will last e.t.c. PD individuals have difficulty managing symptoms such as loss of control and uncertainty. Often these symptoms may be exacerbated by the lack of perceived locus of control, an accentuated fear response and a perceived threat to either interoceptive or exteroceptive stimuli. This heightened anxiety in panic sufferers may be an
antecedent to catastrophic misinterpretation which leads to the exacerbation and maintenance of the vicious cycle of panic (Barlow & Craske, 2007).

Anxiety and panic cognitions were also factors identified by the qualitative study which comprised the following themes: predictive and catastrophic thinking, racing thoughts and worrying. There is considerable evidence that panic cognitions and catastrophic cognitions facilitate the maintenance of PD (Clark, 1988; Bouton et al., 2001; Salkovskis et al., 1996). Participants reported a preoccupation with overthinking and worrying about things potentially going wrong, predicting what is about to happen and thinking the worst. Furthermore, they reported difficulties with managing the racing thoughts before and during the onset of a PA. Tangential thinking and predictive, catastrophic thinking was identified as challenging, by PD participants. These cognitive symptoms are often experienced during the PA and are often reported concurrently with mind racing by PD individuals. Worrying was another significant contributing factor to their PAs which clinical participants identified as challenging when managing their panic thoughts and anxiety symptoms. Some clinical participants reported that excessive worrying could initiate a PA or exacerbate one that has already taken place. Our findings support those of Raffa, White and Barlow (2010) who proposed that cognitions play a central role in PD. Khawaja and Oei (1998) in their systematic review provided substantial empirical evidence in support of the cardinal role catastrophic cognitions play in the maintenance of PD and agoraphobia. This provides compelling evidence for the cognitive theory models which propose that symptoms are maintained by the catastrophic misinterpretation of both internal and external cues made by patients (Craske & Barlow, 2007).
According to modern learning theory anxiety is seen as a distinct construct to panic, where anxiety is characterized by apprehension, worry and tension whilst panic is accompanied by strong autonomic arousal, extreme fear and fight or flight response tendencies (Barlow, 1988; Bouton et al., 2001; Craske, 1999). According to this perspective, a central factor in the development of PD is the interaction of anxiety and panic. Anxiety may manifest as anticipatory anxiety and thus contributes to PD maintenance via a positive feedback loop of anxiety and panic (Barlow, 2000; Öhman et al., 2001). In the current study clinical participants reported experiencing challenges with managing cognitive symptoms of anxiety as well as physiological symptoms of anxiety, hence the ongoing interaction of these two constructs (panic/anxiety) during a PA or in the anticipation of it, appears to be challenging for PD sufferers.

Physiological symptoms of anxiety are another contributing factor that comprises cardiorespiratory symptoms and vestibular symptoms. Coping with cardiorespiratory symptoms associated with anxiety and panic were described as major challenges by clinical participants. Specifically, difficulties with breathing, choking sensations, heart racing or chest pounding, numbness and tingling sensations were amongst some of the symptoms participants reported having difficulty managing. Amongst some of the vestibular symptoms which were commonly reported as being difficult to manage were feelings of faintness, dizziness, hot flushes, shakiness and trembling. PD sufferers have difficulty managing these symptoms as they are likely to perceive these symptoms as threatening and are likely to think that something is terribly wrong with them. These findings support previous research that has found the construct of anxiety sensitivity to be related to PD (McNally, 1994;
Reiss, 1991). Anxiety sensitivity posits that cognitive misappraisals is central to the provocation of anxiety. Individuals who score high on anxiety sensitivity attribute the abovementioned cardiorespiratory and vestibular symptoms experienced by the participants as being dangerous and having inherent beliefs about the possible harm such symptoms to their body or to their mental health (McNally, 1994; Reiss, 1991; Schmidt et al., 1997, 1999; Weems, Hayward, Killen & Taylor, 2002, Dixon et al., 2013). Furthermore, PD participants that reported respiratory symptoms, such as breathing difficulties, choking sensations, heart racing or chest pounding, numbness and tingling sensations, experienced challenges with managing these symptoms. This is consistent with previous findings (Freire et al., 2013; Nardi et al., 2006; Valenca, Nardi, Nascimento, Zin & Versiani, 2002).

7.5.2 Strategies used to manage anxiety and panic thoughts and symptoms

Cognitive strategies are a key theme used to manage anxiety and panic thoughts and symptoms, comprising the following categories: thought stopping, self-talk and reassurance, psychoeducation, distraction and refocus strategies. Thought stopping techniques are amongst one of the most common strategies that are reportedly used to stop the mind racing or the negative spiralling of the anxious thoughts. Such strategies have included dismissing or disputing negative catastrophic thoughts. Participants expressed having some difficulty with thought stopping techniques, when they are having a panic attack, suggesting that they are merely effective.
Self-talk and reassurance were other strategies participants employed to assist them in managing anxiety and panic symptoms. Participants reported practicing positive self-talk, reassuring the self that nothing bad will happen or telling the self that it will pass. Using repeated self-talk that is comforting, and reiterating to the self that it will be okay and that there is nothing to worry about, and to ride the wave are amongst some of the techniques that fall under this category. The strategies used by the participants in Study 2 are amongst the techniques commonly applied in many of the cognitive treatments (Leahy, Holland & McGinn, 2011). In depressed patients with comorbid panic attacks (PAs), Goldberg (2011) proposed that they are given advice about not leaving the place immediately where the panic attack occurred. Furthermore, they were encouraged to practice helpful self-talk and to remind themselves that they have had PAs previously and that they will pass. Reassurance was a strategy used, as well as counteracting negative thoughts with more comforting thoughts, to make the PAs easier to deal with, and less likely to become worse (Goldberg, 2011). Similarly, positive self-talk was reportedly used in a similar way by the participants in Study 2.

Among the strategies discussed, clinical participants mentioned psychoeducation to be helpful, which involved learning about their conditions and themselves as helpful in managing their panic and anxiety. Psychoeducation is a key component of cognitive behavioural therapy and breathing retraining (Craske et al., 2014). Participants reported that educating themselves about the symptoms and that the symptoms are not dangerous is common in the management of anxiety and panic symptoms.
Many clinical participants described the use of distraction techniques and trying to refocus their thoughts. Distraction techniques, included changing one’s environment or having someone distract them, trying to focus on something else, on a single thought or on breathing. These strategies were reportedly used to distract the self from the mind racing and from focusing on catastrophic thinking and panic symptoms. Common distraction techniques included: playing an instrument, or reading a book, messing around on the computer, drawing, colouring and zoning out. The qualitative data supported the notion that although some of the CBT strategies used to assist with the management of panic and anxiety symptoms, they remain quite limited. This appears to be in line with the ideas of Craske et al. (2014) and Hoffman and Smits (2008) who proposed that CBT is still far from optimal.

7.5.3 Physical Strategies

Breathing techniques were amongst the physical strategies used to manage anxiety or panic symptoms. Many participants reported feeling a sense of being so overwhelmed by their symptoms that they lose touch with reality. Practicing deep diaphragmatic breathing yielded mixed results, with some participants finding it helpful and with others noting the limitations of breathing exercises to assist with their panic symptoms. Breathing retraining has proven to be effective however it needs to be practiced as a preventative strategy on a regular basis, rather than on the onset of panic to reverse the symptoms (Garssen, de Ruiter & van Dyck, 1992; Lum, 1983; Grossman et al., 1985). It was difficult to determine whether participants in our study practice deep breathing on a regular basis, as this was not explored in the interview.
Breathing retraining is commonly used in the treatment of panic disorder to purposefully reduce anxious arousal (Barlow & Craske, 2007). Although several studies suggest that this intervention is effective in reducing both panic frequency, and severity (Clark, Salkovskis & Chalkley, 1985; Rapee, 1985; Salkovskis, Jones & Clark, 1986), concerns have been raised about its efficacy when used routinely (Bonn, Readhead & Timmons 1984; Barlow, 2002; Schmidt et al., 2000; Taylor, 2001).

Some theorists have cautioned against the regular use of breathing retraining, postulating that it is counterproductive as it can take on the role of a safety cue or an aid, to the extent that it prevents patients from learning that their catastrophic beliefs are irrational (Taylor, 2010). Safety behaviours are thought to maintain clinical anxiety by exacerbating or maintaining hypervigilance toward threat and increasing the perception that exposure to anxiety-related body sensations is dangerous (Telch et al. 2008). Numerous reports in the literature support the notion that treatment response is improved by the identification and elimination of safety behaviours (e.g., Morgan & Raffle, 1999; Salkovskis, Clark, Hackmann, Wells & Gelder 1999; Schmidt, Richey, Maner & Woolaway-Bickel, 2006; Wells et al., 1995) hence cautioning against breathing retraining. Furthermore, in the one single placebo study conducted by Hibbert and Chan (1989), the effects of breathing retraining on panic attack (PA) frequency and severity were not demonstrated to exceed those produced by a credible placebo. This may be due to the challenges of not knowing the effects of more commonly applied breathing retraining techniques and that the distinction between safety behaviours and coping aids is difficult to determine in clinical practice (Thwaites & Freeston, 2005).
According to numerous theorists, breathing retraining may be an effective intervention for reducing anxious arousal (Clark et al., 1985; Meuret et al., 2008; Rapee, 1985; Salkovskis et al., 1986). Growing evidence has been pointing to capnometry assisted respiratory training, aimed at gaining respiratory control, as showing more promise (e.g., Meuret, Wilhelm, Ritz & Roth, 2008). Both breathing retraining and capnometry assisted respiratory training (CART) are thought to increase perceptions of control in anxiety sufferers, with CART yielding more consistent results (Sanderson et al., 1989).

According to Lickel et al. (2010), the addition of breathing retraining when compared to psychoeducation alone did not improve anxiety sensitivity symptoms, nor add to the gains observed on measures of coping (e.g., perceived control). Our findings from the qualitative interviews suggest that although breathing retraining may be commonly applied by participants, both during a PA and/or routinely as a preventative strategy, there were mixed reports of whether they found the breathing retraining to be helpful. Some of the perceived challenges included that breathing was difficult to practice and that it didn’t always work. Also, it is quite common to experience relaxation-induced anxiety when people with anxiety sensitivity practice breathing exercises and relaxation techniques (Wells, 1990).

Physical activity was another strategy discussed by clinical participants, that was used to manage panic and anxiety symptoms. Participants reported exercising and trying to keep physically active which included walking, pacing, running and stretching. Reports in the literature have demonstrated that people who are regarded to be physically active, and engage in regular physical exercise (2-3 times per week)
have decreased prevalence of anxiety disorders (Goodwin, 2003; Muhsen, Lipsitz, Garty-Sandalon, Gross & Green, 2008; Ströhle et al., 2007; ten Have, de Graaf & Monshouwer, 2011). Although physical exercise has been demonstrated to reduce anxiety symptoms in participants with elevated anxiety levels (Petruzzello, Landers, Hatfield, Kubitz & Salazar, 1991), few studies have explored the use of physical exercise as a treatment for PD (Martinsen, Sandvik & Kolbjørnsrud, 1989; Broocks, et al., 1998; Hovland et al., 2012). A number of studies have demonstrated that physical exercise can have acute anti-panic effects, reducing the risk of PAs in not only healthy individuals (Esquivel, Schruers, Kuipers, & Griez, 2002; Smits et al., 2009; Ströhle et al., 2005) but in patients with high anxiety sensitivity (Broman-Fulks, Berman, Rabian & Webster, 2004; Broman-Fulks & Storey, 2008; Smits et al., 2008) and in patients with PD (Esquivel et al., 2008; Ströhle et al., 2009) with limited prescribed physical exercise. Hovland et al. (2012) compared physical exercise in groups to group cognitive behaviour therapy (CBT) as a treatment for PD in a randomised clinical trial (RCT) and found CBT to be superior yielding significantly better long-term effects than physical exercise which still displayed relatively large effect sizes. Our findings suggest that although physical exercise was used by the PD participants as a strategy to aid their symptoms, they explicated that exercise was still quite limited in terms of its efficacy and utility. Moreover, participants reported that it was difficult to find the time and to maintain the exercise routine.

7.5.4 Mindfulness Strategies

Using the practices of mindfulness and acceptance were discussed by many clinical participants as a strategy that they employ to assist in the management of anxiety and panic symptoms. Observing and noticing thoughts, bodily sensations and
feelings, practicing mindfulness breathing, relaxation and acceptance were amongst the strategies used by participants in this category. Some participants described riding the wave and allowing anxiety to do its thing whilst others reported practicing self-talk in a mindful way whilst pushing through and persevering. Focusing on things on the external environment as well as bodily sensations in a mindful way were also strategies used when experiencing panic or anxiety. The consensus in our clinical group was that some participants found it helpful whereas others practiced but did not find the mindfulness strategies as helpful.

Insights from our qualitative interviews were in line with those documented in the literature as the clinical participants experienced mindfulness without active avoidance and suppression (Levitt et al., 2004) but rather trying to fully experience the emotions of anxiety during a PA in a non-judgemental way. Although some reported finding these strategies beneficial, many reported experiencing challenges with mindfulness in managing their symptoms. This appears to be in line with reports in the literature that suggest that mindfulness strategies and ACT were no better than established treatments (Powers et al., 2009).

Whilst mindfulness was most commonly discussed, some clinical participants in our second study specifically identified meditation as a strategy to manage anxiety and panic symptoms. Prayer meditation and more general meditation were amongst the techniques reportedly used by the participants in Study 2. Meditation practices such as prayer meditation, gratitude meditation, and self-compassion meditation are becoming more increasingly popular, however, there are some limitations with these
strategies, as during a PA it is difficult to engage in these. More empirical evidence is needed for meditation strategies.

### 7.5.5 Experience of the Cold facial Immersion

The initial experience of CFI was described as positive by both clinical and control participants. Although there was some anticipatory anxiety or discomfort related to the breath-hold, and the temperature of the cold water, participants in both groups described a feeling of calmness and relaxed feelings associated with the CFI. A number of participants reported that they relaxed so much that they felt that their heart reduced. Similarly, both groups had similar experiences post CFI, describing it as a pleasant mindful experience that elicited feelings of calmness, relaxation, and stillness. A number of participants described feeling surprised at how relaxed they felt, and how the mind and the anxious thoughts had cleared. From the data gathered from the qualitative interviews, the CFI task was referred to as a mindful experience that was rejuvenating. Interestingly, this is consistent with anecdotal evidence that suggests that free diving is a mindful experience, one that’s characterised as being fully present, and feeling invigorated, energised, calm and relaxed.

In regards to practicing CFI on a regular basis, participants in the clinical group expressed that they were hopeful that the CFI would help with their anxiety. Moreover, many of the participants did suggest that they would practice this on a regular basis, given that they found the CFI was beneficial in reducing their panic and anxiety symptoms when practiced during the experimental study. Both groups felt they had a reduction of anxiety as a result of the CFI and described that they felt a sense of confidence and feeling of empowerment by completing the CFI, particularly
when they surprised themselves that they could hold their breath for that 30 seconds and with feeling so relaxed.

When asked about perceived challenges accessibility and convenience including trying to access water and being worried about what other people think, or feeling embarrassed to use the CFI task in front of others, were amongst the most common barriers explained by both groups. The clinical group differed in the responses as they identified more physical challenges such as not being able to hold breath for 30 seconds, or water being too cold. Time challenges were also identified as a potential barrier, partly the time taken to set up the CFI task, as that may take on average a few to several minutes, as well as time taken to practice. A number of clinical participants perceived the time taken to set up the CFI task as a positive factor as it may be considered a distraction from the panic symptoms. Despite the abovementioned challenges that both groups could foresee with the CFI task most participants were willing to practice it when having a PA.

In respect to the utility of CFI task, both the clinical and control group participants emphasised overall the simplicity and practicality of the CFI, its ability to induce a mindful, invigorating and relaxed state, and its potential to be an effective intervention for anxiety and stress management. Given its practicality, participants stated that they would recommend it to friends and family, given that it is easily applied and so immediately beneficial.

Both clinical and control participants in the study were also asked which ways they would prefer to activate the DR. Amongst some of the most frequent responses
of preferences in how to activate the DR included CFI, splashing cold water in face, having a cold shower, applying an ice pack on the face, and wearing a specially designed facial mask that activates the DR. Participants suggested that a facial mask would be more accessible, something that one can carry with them wherever they go. When one experiences a PA, they could wear the facial mask and activate it so it cools the sensitive areas of the face that activate the DR.

7.5.6 Study Limitations

A limitation of the qualitative study was that the interviews were quite short ranging from 10-20 minutes. This was initially because some participants did not answer the questions of the interview in length, and did not elaborate on their answers much when probed. The researchers were also mindful of the time the participants dedicated to this research study and did not want to take too long with the interviews, as this would have exceeded the time that we informed participants it is likely to take.

Another noted limitation is that the cold water in both our studies was regulated between 7 °C - 12°C whilst maintaining the room temperature at a constant 22°C. Although reports in the literature suggest that lower water temperatures (0°C - 10°C) increases both minute ventilation and elicit more pronounced bradycardia as compared to warmer water (Schagatay & Holm, 1996; Anderson et al., 2016), reports that water was too cold or that it created physical discomfort were discussed by participants. Reports of physical discomfort caused by the cold water temperature have also been noted in the literature (Manley, 1990). An improvement for future studies may be to use cold water temperature ranging 10°C – 15 °C as research indicates facial cold receptors are strongly stimulated by immersion in water with this
temperature range (Daly, 1997; Jay, Christensen & White, 2007). This warrants further investigation to identify if you can elicit the same bradycardiac response in 10°C – 15 °C water without participants experiencing pain and physical discomfort.

Furthermore, control participants were asked the same questions as the clinical group. The questions regarding panic and anxiety symptoms and cognitions did not yield useful information as control participants did not suffer from panic symptoms.

Future methodological considerations for the acquisition of the qualitative data may include more in-depth and comprehensive interviews, and reconsideration of whether to interview control participants. The inclusion of the control group in the interview process, may not be required given that we are more interested in responses that elicit information about panic symptoms experienced by the clinical participants and the utility and application of the CFI task to assist a PD patient with managing panic symptoms. Furthermore, more questions exploring the strategies that are currently being used by clinical participants to manage their symptoms, i.e., how frequently are they practicing the strategies? how effective are they?, and what are the challenges with practicing these strategies? Furthermore, collecting more information about the application of the DR and CFI, and preferences of how and when to use it may assist us further with gathering more comprehensive information about its utility and potentially future directions as a new treatment approach.
7.5.7 Implications and Conclusions

The findings of the qualitative exploration indicate that CFI induces calming, relaxing and anxiolytic effects in both panic and control participants. This is likely to be the case, as CFI activates the DR which is an innate human adaptation that has an oxygen conserving effect and has the ability to reduce the heart rate considerably and to redistribute blood to the most vital organs for survival, including heart and brain. The CFI is also described as a mindful experience, that is very still, and participants reported feeling very present and focused during the task, and invigorated and rejuvenated once they complete the CFI. Participants reported that it is easy to use and practical and that they are likely to use it on a regular basis particularly if it is effective. Although there were some perceived challenges around accessibility, the majority of participants were intrigued regarding its subsequent calming effects and its practicality, and ease of applicability. Moreover, participants were intrigued about the alternative methods one could use to activate the DR. Hence they reported that they are likely to use it, given that they reported that it was surprisingly beneficial. This appears to demonstrate promise as an anxiety management technique and warrants further investigation.
Chapter 8

OVERALL CONCLUSIONS

The present research was presented in three parts, preliminary study, an investigation of cold facial immersion (CFI) and its effects on CO₂ sensitivity, and qualitative exploration of panic and CFI. The preliminary study examined the differences in anxiety and panic symptoms, and cardiorespiratory measurements between the control and clinical participants in a number of challenges, including two breath-hold challenges, a CO₂ challenge, a CFI task, and a CO₂ challenge followed by a CFI task. The second study investigated the effects of CFI on CO₂, particularly whether CO₂ sensitivity may be altered by one single administration of CFI. The qualitative investigation gathered qualitative data via face to face interviews from the same participants given that this is a preliminary investigation on determining whether the DR activated by the CFI warrants further investigation as a potential new treatment or strategy used to manage panic and anxiety symptoms in individuals suffering from panic disorder (PD). The final section of this chapter brings together the findings from the abovementioned studies and discusses their implications for PD research and clinical practice.

In the preliminary study, the key findings were that both clinical and control participants experienced a reduced heart rate (HR) in response to the CFI task. Furthermore, both clinical and control participants experienced a significant heart rate (HR) reduction in response to the CFI task, with the clinical participants experiencing a greater reduction in HR during the CFI task, immediately after the CO₂ challenge.
than the control cohort. This suggests that the DR is a powerful physiological adaptation. This is in line with previous research that has found that the DR is augmented by the CFI task or by facial cooling (Yadav et al., 2017; Khurana & Wu, 2006, Schagatay, 2009). Finally, the preliminary study found that activating the DR via the CFI task, reduced panic cognitions and physiological symptoms of anxiety and panic. This demonstrates some promise in terms of the CFI’s utility to assist with the management and reduction of anxiety and panic symptoms.

There was no significant difference noted in breath-hold (BH) ability between the clinical and the control group. Although the means of the BH durations were slightly shorter for the clinical participants as compared to control participants, in both the passive exhalation BH and the maximum deep inhalation BH, the difference was not significant. Previous studies have yielded varied findings (van der Does, 1997; Asmundson & Stein, 1994; Roth et al., 1998; Zandbergen et al, 1992, Nardi et al, 2002). The inconsistent results found in previous studies may be explained by many of the studies comprising small, heterogeneous samples, diverse inclusion and exclusion criteria, and different PA criteria. It is inconclusive whether our data support Klein’s theory and whether our findings support that the BH challenge may be a marker for CO2 hypersensitivity to CO2 induced panic. Hypersensitivity to CO2 may be more notable in the PD respiratory subtype, something our study could not investigate due to the limitation of having a small sample. The preliminary study reported no significant differences between the clinical and control group, however, an increase was noted in HR in both the clinical group and the control group. Furthermore, the preliminary study reported no significant difference in respiration rates were observed between the clinical group and the control group in response to
the CO₂ challenge. Although previous research examining RR post CO₂ has yielded mixed findings, our findings do not lend support to those of Griez & Van det Hout, (1983; 1986), Klein, (1993), and Schimitel et al. (2012) as our hypothesis was not supported.

The preliminary study findings indicated that the clinical and control participants reported experiencing more anxiety and panic symptoms in response to the CO₂ challenge on the following anxiety measures PACQ, ASI, API, BAI, STAI and VAS –P participant and VAS-R researcher ratings. This appears to be in line with previous research which has reported increased anxiety symptoms following the CO₂ challenge (Beck, Ohtake & Shipherd, 1999; Battaglia et al., 1995).

The results of the investigation of the effects of CFI on CO₂ sensitivity found there were no differences in the physiological response of the CO₂ challenge, as measured by changes in HR and RR. Although appropriate steps and measures were taken to improve the experimental design, it appears that there continued to be some difficulties in this study, particularly with the provocation challenge. It was observed during the procedure in both studies that clinical participants had difficulty with not only taking a maximal deep inhalation of 35% CO₂ and 65% O₂ but also with holding the breath for 4 seconds before exhalation.

Another important finding of the second study was that there was a significant reduction in reported symptoms in the anxiety measures, in both the clinical and the control group. These findings were of particular interest. Although the current study was unable to identify whether one single administration of the CFI task can reduce
CO₂ sensitivity, it appears promising as an intervention given that it was able to significantly reduce self-reported anxiety symptoms in both groups, particularly in the clinical group. Whilst the control group has minimal symptoms overall in response to the CO₂ challenge, they also report a reduction in symptoms and calming effects in response to the CFI task. The clinical group demonstrated a reduction in anxiety symptoms, following exposure to the CFI task on all anxiety measures including the ASI, API, STAI, PACQ, BAI, VAS-R and VAS-P. Given these results have been demonstrated from one exposure to the CFI, it is plausible to infer that frequent exposure to the CFI tasks and to breath-holding may be able to reduce CO₂ sensitivity in PD patients over time. Practicing breath-holding and activating the DR through free diving and CFI on a regular basis has been known to have trained effects, and subsequently the capacity to reduce CO₂ sensitivity (Konstandinidou & Chairopoulou, 2017). Reports in the literature have suggested that a blunted hypercapnic response and prolonged breath-hold times have been associated with the benefits of trained effects and repeated apneas (Andersson & Schagatay, 2009; Walterspacher et al., 2011; Roecker et al., 2014, Grassi et al., 1994; Foster & Sheel, 2005).

Another principal finding of the investigation of CFI effects on CO₂ sensitivity was that there was no significant difference found in HR nor RR following the CO₂ challenge. In many ways, the results of this study correspond with the results of the preliminary study. In the second CO₂ challenge we expected that the clinical group will demonstrate a blunted response following the CO₂ administration. Our results were not significant and hence, it cannot be inferred that one single administration of CFI can alter one’s sensitivity to CO₂. Also as anticipated and consistent with the
findings of the preliminary study, both the panic and control group had a significant HR reduction as a result of the CFI.

The results of the qualitative research are consistent with our main findings from the preliminary and second study. That is, that CFI has calming and relaxing effects and that it reduced panic/anxiety symptoms, anxiety sensitivity, panic thoughts and cognitions. The CFI task was able to reverse panic symptoms in clinical participants, that were elicited by the CO₂ challenge. This was evidenced by the significant reductions in self-reported anxiety measures as reported by the clinical participants as well from feedback from the qualitative interviews. Among the themes of the qualitative research is that CFI is described as a mindful and a pleasant experience and that it is easy to use and practical. Both control and clinical participants described this to be beneficial and reported that they are likely to use it on a regular basis and recommend to others. Although there were some perceived challenges around accessibility, the majority of participants were intrigued regarding its subsequent calming effects and reported that they are likely to use it on a regular basis and tell their family and friends about it that suffer from anxiety. This appears to demonstrate promise as an anxiety management technique and warrants further investigation.

A key feature in anxiety disorders is the failure to appropriately extinguish the fear (Hermans et al., 2006; Milad et al., 2006; Pitman, Hin & Rauch, 2001). Individuals suffering from debilitating anxiety disorders have a tendency to avoid fear provoking situations, or stimuli, or to tolerate them with great difficulty, by employing a range of safety behaviours which further maintain PD symptoms and
prevent fear extinction (Lovibond et al., 2008: 2009). Avoidance and the use of safety behaviours may hold patients back from overcoming their fears and from challenging unrealistic beliefs related to their fear (Lovibond et al., 2009). According to Breier, Charney and Heninger (1986), PD with agoraphobia is a fear-based disorder. Research examining the potential differences in fear extinction processes across all anxiety disorders and particularly in the fear based disorders is lacking (Milad et al., 2014). Furthermore, more human and animal research is needed to understand the neural mechanisms involved in fear generalisation and fear extinction, as this may aid exposure-based treatments. Future research should aim to develop innovative and effective behavioural techniques to promote the generalisation of fear extinction in humans, to better inform translational models for the treatment of psychiatric disorders characterised by excessive fear, and anxiety (Dunsmoor & Paz, 2015). Hence longitudinal studies are needed to investigate both the clinical applicability and likely practice effects of CFI in exposure-based treatments aimed to reduce fear generalisation and promote fear extinction.

These findings may help to inform new treatments for PD patients. The CFI task may have significant merit in its applicability to downregulate the fear, given that it reduces the heart rate significantly, and increases in heart rate are among of the scariest of panic symptoms reported by PD sufferers. It is common to use in hospital emergency departments to counteract atrial tachycardia, and the results from our studies point to the CFI task and the DR to being worthy of further investigation in terms of exploring its efficacy in the management or treatment of PAs and PD. Furthermore, the CFI task may be used psycho-educationally and as a behavioural experiment, following a hyperventilation challenge in an attempt to reverse the
physiological symptoms of anxiety and the panic cognitions. Moreover, it may be used as an exercise to demonstrate to panic and anxiety sufferers how not only can someone habituate to the cold water with the facial immersion task, but that they may also be able to habituate to the feared response.

Although in the first study we did not achieve the differences in breath-hold (BH) durations that we anticipated this warrants further investigation. A large sample size needs to be recruited in order to investigate differences in BH duration between the clinical and the control group. Furthermore, given that repetitive breath-hold training (BHT) with short recovery interval periods, has been associated with longer BH times due to the increased time in withstanding the respiratory drive, and diminishing the ventilatory response to hypercapnia (Schagatay et al., 1999), BHT requires further investigation to determine its efficacy as a potential treatment for PD. Future studies should consider looking at whether BHT can change the duration of BH times in PD patients, and potentially changing the CO\textsubscript{2} sensitivity in this patient group.

In summary, the CFI may be a useful tool diagnostically and therapeutically. The findings from both studies first and foremost indicate the need for further research. The applications of the DR may provide scope for a more effective and robust treatment for PD, given its practicality, and ease of application, when combined with existing treatments such as CBT. Therapies that focus on exposure to feared bodily sensations may be complemented by this powerful autonomic reflex, the DR. Potentially, there may be scope to introduce the DR and CFI applications in self-help, or guided self-help treatments, as a viable combination to provide additional
treatment as well as effective and cost-effective treatment for PD. The feasibility, practicality, and efficacy of such a combination may yield important insights and improved interventions for PD and anxiety sufferers, something future studies will assist to determine.
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Appendix A: Ethics Approval
Dear Michael and Peter,

**SUHREC Project 2014/010 The efficacy of cold facial immersion and the diving response in treating panic disorder**

Prof M Kyrios, Mr P Kyriakoulis et al

Approved Duration: 14/02/2014 To 01/12/2016

I refer to the ethical review of the above project protocol undertaken by Swinburne’s Human Research Ethics Committee (SUHREC). Your responses to the review were put to a SUHREC delegate for consideration and accords with the feedback.

I am pleased to advise that, as submitted to date, the project must commence in line with standard on-going ethics clearance conditions here outlined.

- All human research activity undertaken under Swinburne auspices must conform to Swinburne and external regulatory standards, including the *National Statement on Ethical Conduct in Human Research* and with respect to secure data use, retention and disposal.

- The named Swinburne Chief Investigator/Supervisor remains responsible for any personnel appointed to or associated with the project being made aware of ethics clearance conditions, including research and consent procedures or instruments approved. Any change in chief investigator/supervisor requires timely notification and SUHREC endorsement.

- The above project has been approved as submitted for ethical review by or on behalf of SUHREC. Amendments to approved procedures or instruments ordinarily require prior ethical appraisal/clearance. SUHREC must be notified immediately or as soon as possible thereafter of (a) any serious or unexpected adverse effects on participants and any redress measures; (b) proposed changes in protocols; and (c) unforeseen events which might affect continued ethical acceptability of the project.

- At a minimum, an annual report on the progress of the project is required as well as at the conclusion (or abandonment) of the project.

- A duly authorised external or internal audit of the project may be undertaken at any time.

Please contact the Research Ethics Office if you have any queries about on-going ethics.
clearance, citing the SUHREC project number. Copies of clearance emails should be retained as part of project record-keeping.

Best wishes for the project.

Kind regards,

Ann

____________________________________
Dr Ann Gaeth
Executive Officer (Research)
Swinburne Research (H68)
Swinburne University of Technology
P O Box 218
HAWTHORN VIC 3122
Ph +61 3 9214 8356
Dear Michael and Peter,

**SUHREC Project 2014/010 The efficacy of cold facial immersion and the diving response in treating panic disorder**
Prof M Kyrios, Mr P Kyriakoulis et al
Approved Duration: 14/02/2014 To 01/12/2016
Project Modification: Mar 2014

I refer to your request, as e-mailed on 24 March 2014 with attachments, regarding a modification request replace one module with another.

I am pleased to advise that, as submitted to date, the modified extended project/protocol may continue in line with standard ethics clearance conditions previously communicated and reprinted below.

Please contact me if you have any queries about on-going ethics clearance, citing the SUHREC project number. Copies of clearance emails should be retained as part of project record-keeping.

As before, best wishes for the project.

Regards

Ann

----------------------------------------------------------------------------------------------
Dr Ann Gaeth
Executive Officer (Research)
Swinburne Research (H68)
Swinburne University of Technology
P O Box 218
HAWTWORTH VIC 3122
Ph +61 3 9214 8356
Dear Mike and Peter

**SHR Project 2014/010 The efficacy of cold facial immersion and the diving response in treating panic disorder**

Prof M Kyrios, FHAD; Mr P Kyriakoulis, Prof D Liley, Dr M Schier

Approved Duration: 14/02/2014 To 01/12/2016 [Modified May 2014]

I refer to your request concerning a modification to the above project approved protocol re a change of location for testing and confidential data management. The request, as emailed on 20 May 2014, was put to a SUHREC delegate for consideration.

I am pleased to advise that, as modified to date, the project may continue in line with ethics clearance conditions previously communicated and reprinted below.

Please contact the Research Ethics Office if you have any queries about on-going ethics clearance, citing the project number. A copy of this email should be retained as part of project record-keeping.

As before, best wishes for the project.

Yours sincerely

Keith

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Keith Wilkins
Secretary, SUHREC & Research Ethics Officer
Swinburne Research (H68)
Swinburne University of Technology
P O Box 218
HAWTHORN VIC 3122
Tel +61 3 9214 5218
Fax +61 3 9214 5267
To: Prof David Liley/Mr Peter Kyriakoulis, FHAD

Dear David and Peter

**SHR Project 2014/010 The efficacy of cold facial immersion and the diving response in treating panic disorder**

Prof D Liley, FHAD; Mr P Kyriakoulis, Dr M Schier, Prof M Kyrios

Approved Duration: 14/02/2014 To 01/12/2016
[Modified: March 2014, May 2014, August 2014]

I refer to your request, concerning modifications to the above project approved protocol, as emailed on 24 July 2014 with attachments. The request (re changes to inclusion criteria, research and consent arrangements and also changed supervisory arrangements) was put to SUHREC delegates for consideration and feedback sent to you on 11 August 2014. I acknowledge your response, emailed today, accepting the feedback was regards what has been approved in relation to the modification request.

I am pleased to advise that, as modified and approved to date, the project may continue in line with ethics clearance conditions previously communicated and reprinted below.

Please contact the Research Ethics Office if you have any queries about on-going ethics clearance, citing the project number. A copy of this email should be retained as part of project record-keeping.

As before, best wishes for the project.

Yours sincerely

Keith

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Keith Wilkins
Secretary, SUHREC & Research Ethics Officer
Swinburne Research (H68)
Swinburne University of Technology
P O Box 218
HAWTHORN VIC 3122
Tel +61 3 9214 5218
Fax +61 3 9214 5267
Dear David and Peter

**SHR Project 2014/010 The efficacy of cold facial immersion and the diving response in treating panic disorder**
Prof D Liley, FHAD; Mr P Kyriakoulis, Dr M Schier, Prof M Kyrios
Approved Duration: 14/02/2014 To 01/12/2016

I refer to your request, concerning modifications to the above project approved protocol, as emailed on 16 December 2015 with attachments. The request documentation, re Study 2 and including consent instruments for Study 2, was put to a SUHREC delegate for consideration.

I am pleased to advise that, as modified and approved to date, the project may continue in line with ethics clearance conditions previously communicated and reprinted below. (Information on project self-auditing, reporting and modifications/additions can now be found on the Research Intranet.)

Please contact the Research Ethics Office if you have any queries about on-going ethics clearance, citing the project number. A copy of this email should be retained as part of project record-keeping.

As before, best wishes for the project.

Yours sincerely

Keith

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Keith Wilkins
Secretary, SUHREC & Research Ethics Officer
Swinburne Research (H68)
Swinburne University of Technology
P O Box 218
HAWTHERN VIC 3122
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Appendix B: Plain Language Statement and Consent

Forms Group 1 (Clinical) and Group 2 (Control) for the Preliminary Study
PLAIN LANGUAGE STATEMENT AND CONSENT FORM: GROUP 1

Project Title: The efficacy of cold facial immersion, apnea and the diving response in the treatment of panic symptoms.

Investigators:
Prof. David Liley (Researcher)
Prof. Michael Kynos (Researcher)
Prof. Greg Murray (Researcher)
Dr. Mark Schier (Researcher)
Peter Kyrakoulis (Researcher)

1. Your Consent

You are invited to take part in this research project. This Plain Language Statement contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project so that you can make a fully informed decision whether you are going to participate. Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project.

2. Purpose and Background

We are conducting a study to investigate how activation of the diving response can be used to treat panic symptoms. The diving response is a human adaptation that allows us to endure a lack of oxygen under water. It is activated by apnea (breath-holding) and cold facial immersion (water coming into contact with the face). During the diving response a number of physiological changes occur, one of which is a significant decrease in heart rate. In many ways the physiological adaptations experienced during the diving response are the opposite of those triggered when an individual encounters a panic attack. This study aims to investigate whether cold facial immersion and the physiological responses associated with the diving response can assist individuals in reducing panic symptoms and changing panic cognitions.

In order to investigate the efficacy of cold facial immersion in treating panic we are seeking participants (18 – 55 years old) who suffer from frequent panic attacks, or have Panic Disorder with or without agoraphobia.

The results of this research will be used to help researcher, Peter Kyrakoulis to complete a thesis and obtain a Doctor of Philosophy in Psychology degree.

3. Procedures

Please note that participation in this study is voluntary. Initially participants will be asked to complete a series of psychological tests and two semi-structured interviews which should take approximately half an hour to one hour. Demographical data such as age, gender, and health related information will also be gathered. Those with known respiratory, cardiovascular illness, epilepsy, diabetes, brain haemorrhage/aneurisms or renal disease should not participate. Women who are pregnant or possibly pregnant should not participate. Those with a history of substance dependence/abuse or other mental health issues should advise the researchers, as they may not be able to participate. Additionally we ask participants to abstain from alcohol, cigarettes, other substances and caffeine for a period of 2 hours before the testing. Participants who are diagnosed with Panic Disorder and meet the health screening criteria will be invited to participate in the study. Participants who take medication intermittently for example painkillers, anxiolytics or asthma related medications may be allowed to partake in the study if they pass the health screening test. Participants should bring their medications with them just in case the need arises for them to take medication. The study will involve an
experimental study held at Swinburne University, Hawthorn Campus, in which participants will undergo four tasks which will be randomly assigned, including: a) Two breath holds: the first of which requires participants to exhale and then hold their breath for as long as possible; after a two minute rest period the second breath hold will involve participants taking a deep breath and holding their breath for as long as possible. b) cold facial immersion and 30 seconds apnea. c) one single inhalation of 35%CO2 and 65% O2 and d) one single deep inhalation of 35% CO2 and 65% O2 followed by cold facial immersion. Participants will practice cold facial immersion in response to panic symptoms that may be elicited via the CO2 (Carbon Dioxide) challenge. The cold facial immersion task will involve participants immersing their face in a container of water whilst breath holding for 30 seconds. The CO2 challenge involves participants taking in a single inhalation of a 35% CO2 / 65% O2 (Oxygen) gas mixture and holding their breath for 4 seconds before exhaling. During the CO2 challenge and cold facial immersion tasks your respiration rate and heart rate will be monitored using a Zephyr bio harness which will involve you being fitted with a chest strap and monitored throughout. A finger pulse oximeter will also be used to monitor oxygen saturation in the blood. The laboratory experiment will take approximately 30 - 40 minutes and will also involve the completion of a battery of psychological tests. The laboratory experiment will take approximately 30 - 40 minutes and will also involve the completion of a battery of psychological tests. The Zephyr Bioharness and pulse oximeter equipment are low voltage, battery powered, and make no direct electrical connection to mains power. The pulse oximeter has no electrical contact with the participant. The Zephyr has electrodes which receive electrical signals from participants but do not pass a current through the participant. All equipment planned to be used for this proposal conforms to Australian Standard AS/NZ 3551.2005 "Technical management program for medical devices".

4. Possible Benefits

Although we cannot guarantee or promise that you will receive any benefits from this project, a possible benefit may be the opportunity to trial a new technique that may result in the reduction of panic symptoms. Another benefit that could result through the CO2 challenge is that participants may achieve a desensitisation of panic symptoms as a result of repeated exposure through CO2 inhalation. The findings and outcomes of this research may also further our current understanding of panic disorder and its treatment.

5. Possible Risks

Whilst the possibility of risks is considered minimal, the CO2 challenge is likely to elicit panic like symptoms in participants' with panic disorder, which may cause some distress with some individuals. These sensations are expected to be transient and not harmful. Furthermore given that the researcher is a Clinical Psychologist with vast experience in the area of anxiety and panic, participants will be supported throughout the study.

If you experience concern or distress at any stage of the research there are several ways that you can get help. The researcher is a Clinical Psychologist and will be available to assist with any concerns throughout the entire research process. If you would like to discuss any issues that arise with a counsellor and you are a student at Swinburne you can call Student Counselling Services at Hawthorn on 9214 8882. Students and others living in Melbourne may contact the Swinburne Psychology Clinic on 9214 8653 for low-cost community counselling. If you live in Australia, you may also phone Lifeline on 13 11 14, or online at www.depression.net.com.au or www.reachout.com.au

6. Privacy, Confidentiality and Disclosure of Information

Further any information obtained in connection with this project by researchers and that can identify you will remain confidential. It will only be disclosed with your permission, subject to legal requirements. The information collected from participants during the research project will be stored on computer files. Any identifiable information will be removed, and a code applied, once results are entered into data files. The transcripts will be stored on a computer file which will be password protected. Following project completion the information collected from participants will be stored on

Plain Language Statement & Consent Form: Group 1
Version 2 (22/07/14)
computer files at Swinburne University and will be password protected. This data will be stored for 5 years following final publication of results. In any publication, information will be provided in such a way that you cannot be identified. Individual participants will not be identified in any reports of the study, or publications, as only aggregated data will be reported.

7. Results of Project

A summary of the research results will be available for participants who wish to know the outcome of the research. Should participants wish to obtain information on the results of this research, participants can contact the principal researcher who will provide them with a summary.

Data from this study may be used in future journal publications and conferences.

8. Participation is Voluntary

Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you decide to withdraw from this project, please notify a member of the research team.

9. Complaints

This project has been approved by Swinburne’s Human Research Ethics Committee (SUHREC) in line with the National Statement on Ethical Conduct in Human Research. If you have any concerns or complaints about the conduct of this project, you can contact:

Research Ethics Officer, Swinburne Research (H68), Swinburne University of Technology, P O Box 218, HAWTHORN VIC 3122.
Tel (03) 9214 5218 or +61 3 9214 5218 or resehtics@swin.edu.au

10. Further Information, Queries or Any Problems

If you require further information, wish to withdraw your participation or if you have any problems concerning this project (for example, any side effects), you can contact the principal researcher.

The researchers responsible for this project are:

Prof. David Liley
Principal Researcher
Swinburne University
Faculty of Art, Health and Design
Hawthorn Campus
Email: dliley@swin.edu.au

Peter Kyriakoulis
Student Researcher
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Ph. 0429 998 188
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Plain Language Statement & Consent Form: Group 1
Version 2 (22/07/14)
CONSENT FORM: GROUP 1

Project Title: The efficacy of cold facial immersion, apnea and the diving response in the treatment of panic symptoms.

Investigators:
Prof David Liley (Researcher)
Prof Greg Murray (Researcher)
Prof. Michael Kyrios (Researcher)
Dr. Mark Scher (Researcher)
Peter Kyriakoulis (Researcher)

1. I consent to participate in the project named above. I have been provided a copy of the plain language statement to which this consent form relates and any questions I have asked have been answered to my satisfaction.

2. In relation to this project, please circle your response to the following:
   a) I agree to be interviewed by the researcher
   b) I agree to complete questionnaires asking me about panic cognitions and symptoms
   c) I agree to participate in the laboratory experiment
   d) I agree to make myself available for further information if required

3. I acknowledge that:
   (a) my participation is voluntary and that I am free to withdraw from the project at any time without explanation;
   (b) the Swinburne project is for the purpose of research and not for profit;
   (c) any identifiable information about me which is gathered in the course of and as the result of my participating in this project will be (i) collected and retained for the purpose of this project and (ii) accessed and analysed by the researcher(s) for the purpose of conducting this project;
   (d) my anonymity is preserved and I will not be identified in publications or otherwise without my express written consent.

By signing this document I agree to participate in this project.

Name of Participant: ...........................................................................................................

Signature & Date: ...........................................................................................................
PLAIN LANGUAGE STATEMENT AND CONSENT FORM: GROUP 2

Project Title: The efficacy of cold facial immersion, apnea and the diving response in the treatment of panic symptoms.

Investigators:
Prof David Liley (Researcher)
Prof. Michael Kynios (Researcher)
Dr. Mark Scher (Researcher)
Peter Kyriakoulis (Student Researcher)

1. Your Consent
You are invited to take part in this research project. This Plain Language Statement contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project so that you can make a fully informed decision whether you are going to participate. Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project.

2. Purpose and Background
We are conducting a study to investigate how activation of the diving response can be used to treat panic symptoms. The diving response is a human adaptation that allows us to endure a lack of oxygen under water. It is activated by apnea (breath-holding) and cold facial immersion (water coming into contact with the face). During the diving response a number of physiological changes occur, one of which is a significant decrease in heart rate. In many ways the physiological adaptations experienced during the diving response are the opposite of those triggered when an individual encounters a panic attack. This study aims to investigate whether cold facial immersion and the physiological responses associated with the diving response can assist individuals in reducing panic symptoms.

In order to investigate the physiological changes elicited by the diving response through cold facial immersion we are seeking participants (18 – 55 yrs) who do not currently suffer from mental illness.

The results of this research will be used to help researcher, Peter Kyriakoulis to complete a thesis and obtain a Doctor of Philosophy in Psychology degree.

3. Procedures
Please note that participation in this study is voluntary. Initially participants will be asked to complete a series of psychological tests and two semi-structured interviews which should take 60 – 90 minutes. Demographical data such as age, gender, and health related information will also be gathered.
Participants who meet the health screening criteria and do not currently suffer from mental illness will be invited to participate in the study. The study will involve an experimental study held at Swinburne University, Hawthorn Campus, in which participants will undergo four tasks which will be randomly assigned, including: a) two breath holds: the first of which requires participants to exhale and then hold their breath for as long as possible, after a two minute rest period the second breath hold will involve participants taking a deep breath and holding their breath for as long as possible. b) cold facial immersion and 36 seconds apnea. c) one single inhalation of 35%CO2 and 65% O2 and d) one single deep inhalation of 35% CO2 and 65% O2 followed by cold facial immersion. Participants will practice cold facial immersion in response to panic symptoms that may be elicited via the CO2 (Carbon Dioxide) challenge. The cold facial immersion task will involve participants immersing their face in a

Plain Language Statement & Consent Form: Group 2 Version 2 (22/07/14)
container of water whilst breath-holding for 30 seconds. The CO₂ challenge involves participants taking in a single inhalation of a 35% CO₂ / 85% O₂ (Oxygen) gas mixture and holding their breath for 4 seconds before exhaling. During the CO₂ challenge and cold facial immersion tasks your respiration rate and heart rate will be monitored using a Zephyr bioharness which will involve you being fitted with a chest strap and monitored throughout. A finger pulse oximeter will also be used to monitor oxygen saturation in the blood. The laboratory experiment will take approximately 30 – 40 minutes and will also involve the completion of a battery of psychological tests. The laboratory experiment will take approximately 30 – 40 minutes and will also involve the completion of a battery of psychological tests. The Zephyr bioharness and pulse oximeter equipment are low voltage, battery powered, and make no direct electrical connection to mains power. The pulse oximeter has no electrical contact with the participant. The Zephyr has electrodes which receive electrical signals from participants but do not pass a current through the participant. All equipment planned to be used for this proposal conforms to Australian Standard AS/NZ 3551.2005 “Technical management program for medical devices”.

4. Possible Benefits
Although we cannot guarantee or promise that you will receive any benefits from this project, a possible benefit is the opportunity to learn about the diving response and how it can be activated to lower the heart rate, which consequently could have a relaxing effect.

5. Possible Risks
Whilst the possibility of risks is considered minimal, the CO₂ challenge may elicit anxiety or panic like symptoms and cause distress in some individuals. These sensations are expected to be transient and not harmful. Furthermore, given that the researcher is a Clinical Psychologist with vast experience in the area of anxiety and panic, participants’ will be supported throughout the study.

If you experience concern or distress at any stage of the research there are several ways that you can get help. The researcher is a Clinical Psychologist and will be available to assist with any concerns throughout the entire research process. If you would like to discuss any issues that arise with a counsellor and you are a student at Swinburne you can call Student Counselling Services at Hawthorn on 9214 8882. Students and others living in Melbourne may contact the Swinburne Psychology Clinic on 9214 8653 for low cost community counselling. If you live in Australia, you may also phone Lifeline on 13 11 14, or online at www.depressionet.com.au or www.reachout.com.au

6. Privacy, Confidentiality and Disclosure of Information
Further any information obtained in connection with this project by researchers and that can identify you will remain confidential. It will only be disclosed with your permission, subject to legal requirements. The information collected from participants during the research project will be stored on computer files. Any identifiable information will be removed, and a code applied, once results are entered into data files. The transcripts will be stored on a computer file which will be password protected. Following project completion the information collected from participants will be stored on computer files at Swinburne University and will be password protected. This data will be stored for 5 years following final publication of results. In any publication, information will be provided in such a way that you cannot be identified. Individual participants will not be identified in any reports of the study, or publications, as only aggregated data will be reported.

7. Results of Project
A summary of the research results will be available for participants who wish to know the outcome of the research. Should participants wish to obtain information on the results of this research, participants can contact the principal researcher who will provide them with a summary.

Data from this study may be used in future journal publications and conferences.
8. Participation is Voluntary

Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. Any information obtained from you to date will not be used and will be destroyed.

If you decide to withdraw from this project, please notify a member of the research team.

9. Complaints

This project has been approved by Swinburne's Human Research Ethics Committee (SUHREC) in line with the National Statement on Ethical Conduct in Human Research. If you have any concerns or complaints about the conduct of this project, you can contact:

Research Ethics Officer, Swinburne Research (H168),
Swinburne University of Technology, P O Box 218, HAWTHORN VIC 3122.
Tel (03) 9214 5218 or +61 3 9214 5218 or resethes@swin.edu.au

10. Further Information, Queries or Any Problems

If you require further information, wish to withdraw your participation or if you have any problems concerning this project (for example, any side effects), you can contact the principal researcher.

The researchers responsible for this project are:

Prof. David Liley
Principal Researcher
Swinburne University
Faculty of Life & Social Sciences
Hawthorn Campus
Email: dilley@swin.edu.au

Peter Kyriakoulis
Student Researcher
Swinburne University
Faculty of Life & Social Sciences
Hawthorn Campus
Ph: 0429 998 188
Email: Peter.Kyriakoulis@student.swin.edu.au

Dr. Mark Schier
Associate Researcher
Swinburne University
Faculty of Life & Social Sciences
Hawthorn Campus
Ph: 03 9214 6713
Email: mschier@swin.edu.au

Prof. Michael Kyrios
Principal Researcher
Swinburne University
Faculty of Life & Social Sciences
Hawthorn Campus
Ph: 03 9214 4886
Email: MKyrios@swin.edu.au
CONSENT FORM: GROUP 2

Project Title: The efficacy of cold facial immersion, apnea and the diving response in the treatment of panic symptoms.

Investigators:
Prof. Michael Kyrios (Principal Researcher)
Dr. Mark Schier (Researcher)
Peter Kyriakoulis (Student Researcher)

1. I consent to participate in the project named above. I have been provided a copy of the plain language statement to which this consent form relates and any questions I have asked have been answered to my satisfaction.

2. In relation to this project, please circle your response to the following:
   a) I agree to be interviewed by the researcher

   
   
   b) I agree to complete questionnaires asking me about panic cognitions and symptoms

   
   
   c) I agree to participate in the laboratory experiments

   
   
   d) I agree to make myself available for further information if required

   

3. I acknowledge that:
   
   a) my participation is voluntary and that I am free to withdraw from the project at any time without explanation;

   (b) the Swinburne project is for the purpose of research and not for profit;

   c) any identifiable information about me which is gathered in the course of and as the result of my participating in this project will be (i) collected and retained for the purpose of this project and (ii) accessed and analysed by the researcher(s) for the purpose of conducting this project;

   d) my anonymity is preserved and I will not be identified in publications or otherwise without my express written consent.

By signing this document I agree to participate in this project.

Name of Participant: ..................................................................................................

Signature & Date: ..........................................................................................
Appendix C: Plain Language Statement and Consent Forms Group 1 (Clinical) and Group 2 (Control) for Study 2
PLAIN LANGUAGE STATEMENT AND CONSENT FORM: GROUP 2

Project Title: The efficacy of cold facial immersion, apnea and the diving response in the treatment of panic symptoms.

Investigators:
Prof. David Liley (Researcher)
Prof. Michael Kynns (Researcher)
Prof. Greg Murray (Researcher)
Dr. Mark Scher (Researcher)
Peter Kynkoulis (Researcher)

1. Your Consent
You are invited to take part in this research project. This Plain Language Statement contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project so that you can make a fully informed decision whether you are going to participate. Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project.

2. Purpose and Background
We are conducting a study to investigate how activation of the diving response can potentially be used to reduce panic symptoms. The diving response is a human adaptation that allows us to reduce a lack of oxygen under water. It is activated by apnea (breath holding) and cold facial immersion (water coming into contact with the face). During the diving response, a number of physiological changes occur, one of which is a significant decrease in heart rate. In many ways the physiological adaptations experienced during the diving response are the opposite of those triggered when an individual encounters a panic attack. This study aims to investigate whether cold facial immersion and the physiological responses associated with the diving response can assist individuals in reducing panic symptoms.

In order to investigate the physiological changes elicited by the diving response through cold facial immersion we are seeking participants (18 – 55 yrs) who do not currently suffer from mental illness.

The results of this research will be used to help researcher, Peter Kynkoulis, to complete a thesis and obtain a Doctor of Philosophy in Psychology degree.

3. Procedures
Please note that participation in this study is voluntary. Initially participants will be asked to complete a series of psychological tests and two semi-structured interviews which should take 90 – 90 minutes. Demographic data such as age, gender, and health related information will also be gathered. Participants who meet the health screening criteria and do not currently suffer from mental illness will be invited to participate in the study. The study will involve an experimental study held at Swinburne University, Hawthorn Campus. In the first stage of the study, participants will complete some anxiety measures before and after undergoing a single inhalation of 35% CO₂ and 65% O₂. In the second stage (a few days to a week later depending on your availability), participants will undergo a cold facial immersion (CFI) task followed by a single deep inhalation of 35% CO₂ and 65% O₂ (CO₂ Challenge). The CFI task will involve participants immersing their face in a container of water whilst breath-holding for 30 seconds. The CO₂ challenge involves participants taking in a single inhalation of a 35% CO₂ / 65% O₂ gas mixture and holding their breath for 4 seconds before exhaling. During the CO₂ challenge and CFI tasks participants’ respiration rate and heart rate will be monitored using a
Zephyr bioharness which will involve being fitted with a chest strap and monitored throughout. The final stage will involve a follow-up phone call to receive some feedback on the cold facial immersion task which will be conducted two days later. Feedback will be conducted via completing a brief survey over the phone. All the above-mentioned stages of the laboratory experiment will take approximately 45-60 minutes combined and will also involve the completion of a battery of psychological tests. The Zephyr bioharness and pulse oximeter equipment are low voltage, battery powered, and make no direct electrical connection to mains power. The pulse oximeter has no electrical contact with the participant. The Zephyr has electrodes which receive electrical signals from participants but do not pass a current through the participant. All equipment planned to be used for this proposal conforms to Australian Standard AS/NZ 3951.2009 “Technical management program for medical devices”.

4. Possible Benefits
Although we cannot guarantee or promise that you will receive any benefits from this project, a possible benefit is the opportunity to learn about the body's response and how it can be activated to lower the heart rate, which consequently could have a relaxing effect.

5. Possible Risks
Whilst the possibility of risks is considered minimal, the CO2 challenge may elicit anxiety or panic-like symptoms and cause distress in some individuals. These sensations are expected to be transient and not harmful. Furthermore, given that the researcher is a Clinical Psychologist with vast experience in the area of anxiety and panic, participants will be supported throughout the study.

If you experience concern or distress at any stage of the research there are several ways that you can get help. The researcher is a Clinical Psychologist and will be available to assist with any concerns throughout the entire research process. If you would like to discuss any issues that arise with a counselor and you are a student at Swinburne you can call Student Counselling Services at Hawthorn on 9214 8887. Students and others living in Melbourne may contact the Swinburne Psychology Clinic on 9214 9665 for low-cost community counseling. If you live in Australia, you may also phone Lifeline on 13 11 14, or online at www.depressionnet.com.au or www.reachout.com.au

6. Privacy, Confidentiality and Disclosure of Information
Further any information obtained in connection with this project by researchers and that can identify you will remain confidential. It will only be disclosed with your permission, subject to legal requirements. The information collected from participants during the research project will be stored on computer files. Any identifiable information will be removed, and a code applied, once results are entered into data files. The transcripts will be stored on a computer file which will be password-protected. Following project completion the information collected from participants will be stored on computer files at Swinburne University and will be password-protected. This data will be stored for 5 years following final publication of results. In any publication, information will be provided in such a way that you cannot be identified. Individual participants will not be identified in any reports of the study, or publications, as only aggregated data will be reported.

7. Results of Project
A summary of the research results will be available for participants who wish to know the outcome of the research. Should participants wish to obtain information on the results of this research, participants can contact the principal researcher who will provide them with a summary.

Data from this study may be used in future journal publications and conferences.

Plain Language Statement & Consent Form: Group 2
Version 3 (14/12/16)
8. Participation is Voluntary
Participation in any research project is voluntary. If you do not wish to take part you are not
obliged to. If you decide to take part and later change your mind, you are free to withdraw from the
project at any stage. Any information obtained from you to date will not be used and will be destroyed.
If you decide to withdraw from this project, please notify a member of the research team.

9. Complaints
This project has been approved by Swinburne's Human Research Ethics Committee (SUHREC) in line
with the National Statement on Ethical Conduct in Human Research. If you have any concerns or
complaints about the conduct of this project, you can contact:

Research Ethics Officer, Swinburne Research (HRI),
Swinburne University of Technology, P O Box 218, HAWTHORN VIC 3122,
Tel (03) 9214 5218 or +61 3 9214 5216 or research.ethics@swin.edu.au

10. Further Information, Queries or Any Problems
If you require further information, wish to withdraw your participation or if you have any problems
concerning this project (for example, any side effects), you can contact the principal researcher.

The researchers responsible for this project are:

Prof. David Lilley
Principal Researcher
Swinburne University
Faculty of Life & Social Sciences
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Email: dilliey@swin.edu.au

Peter Kynakoulis
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Dr. Mark Schier
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Prof. Greg Murray
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Prof. Michael Kynns
Principal Researcher
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Faculty of Life & Social Sciences
Hawthorn Campus
Ph: 03 9214 4886
Email: MKynns@swin.edu.au
CONSENT FORM: GROUP 2

Project Title: The efficacy of cold facial immersion, apnea and the diving response in the treatment of panic symptoms.

Investigators:
Prof. David Lilly (Researcher)
Prof. Michael Kynns (Researcher)
Prof. Greg Murray (Researcher)
Dr. Mark Schier (Researcher)
Peter Kyriakoulis (Researcher)

1. I consent to participate in the project named above. I have been provided a copy of the plain language statement to which this consent form relates and any questions I have asked have been answered to my satisfaction.

2. In relation to this project, please circle your response to the following:
   a) I agree to be interviewed by the researcher Yes No
   b) I agree to complete questionnaires asking me about panic cognitions and symptoms Yes No
   c) I agree to participate in the laboratory experiments Yes No
   d) I agree to make myself available for further information if required Yes No

3. I acknowledge that:
   a) my participation is voluntary and that I am free to withdraw from the project at any time without explanation;
   b) the Swinburne project is for the purpose of research and not for profit;
   c) any identifiable information about me which is gathered in the course of and as a result of my participating in this project will be (i) collected and retained for the purpose of this project and (ii) accessed and analysed by the researcher(s) for the purpose of conducting this project;
   d) my anonymity is preserved and I will not be identified in publications or otherwise without my express written consent.

By signing this document I agree to participate in this project.

Name of Participant: .................................................................

Signature & Date: .................................................................
PLAIN LANGUAGE STATEMENT AND CONSENT FORM: GROUP 1

Project Title: The efficacy of cold facial immersion, apnea and the diving response in the treatment of panic symptoms.

Investigators:
Prof. David Wiley (Researcher)
Prof. Michael Kynics (Researcher)
Prof. Greg Murray (Researcher)
Dr. Mark Schier (Researcher)
Peter Kyriakoulis (Researcher)

1. Your Consent
You are invited to take part in this research project. This Plain Language Statement contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project so that you can make a fully informed decision whether you are going to participate. Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project.

2. Purpose and Background
We are conducting a study to investigate how activation of the diving response can potentially be used to reduce panic symptoms. The diving response is a human adaptation that allows us to endure a lack of oxygen underwater. It is activated by apnea (breath-holding) and cold facial immersion (water coming into contact with the face). During the diving response, a number of physiological changes occur, one of which is a significant decrease in heart rate. In many ways, the physiological adaptations experienced during the diving response are the opposite of those triggered when an individual encounters a panic attack. This study aims to investigate whether cold facial immersion and the physiological responses associated with the diving response can assist individuals in reducing panic symptoms and changing panic cognitions.

In order to investigate the efficacy of cold facial immersion in treating panic, we are seeking participants (18 to 65 years old) who suffer from infrequent panic attacks, or have Panic Disorder with or without agoraphobia.

The results of this research will be used to help researcher, Peter Kyriakoulis, to complete a thesis and obtain a Doctor of Philosophy in Psychology degree.

3. Procedures
Please note that participation in this study is voluntary. Initially participants will be asked to complete a series of psychological tests and two semi-structured interviews which should take approximately half an hour to one hour. Demographical data such as age, gender, and health-related information will also be gathered. Those with known respiratory, cardiovascular illness, epilepsy, diabetes, brain haemorrhage/menorrhagias or renal disease should not participate. Women who are pregnant or possibly pregnant should not participate. Those with a history of substance dependence/abuse or other mental health issues should advise the researchers, as they may not be able to participate. Additionally, we ask participants to abstain from alcohol, cigarettes, other substances and caffeine for a period of 2 hours before the testing. Participants who are diagnosed with Panic Disorder and meet the health screening criteria will be invited to participate in the study. Participants who take medication intermittently for example painkillers, antidepressants or asthma related medications may be allowed to participate in the study if they pass the health screening test. Participants should bring their medications with them just in case the need arises for them to take medication. This study will involve an...
experimental study held at Swinburne University, Hawthorn Campus. In the first stage of the study participants will complete a number of anxiety measures before and after undergoing one single
inhalation of 35% CO₂ and 65% O₂. In the second stage (a few days to a week later depending on
your availability), participants will undergo a cold facial immersion (CFI) task followed by one single
depth inhalation of 35% CO₂ and 65% O₂ (CO₂ Challenge). The CFI task will involve participants
immersing their face in a container of water whilst breath holding for 30 seconds. The CO₂ challenge
involves participants taking a single inhalation of a 35% CO₂ / 65% O₂ gas mixture and holding their
breath for 4 seconds before exhaling. During the CO₂ challenge and CFI tasks participant’s
respiration rate and heart rate will be monitored using a Zephyr bio harness which will involve being
fitted with a chest strap and monitored throughout. The final stage will involve a follow up phone call to
receive some feedback on the cold facial immersion task which will be conducted two days later.
Feedback will be conducted via completing a brief survey over the phone. All the abovementioned
stages of the laboratory experiment will take approximately 45-60 minutes combined and will also
involve the completion of a battery of psychological tests. The Zephyr Bioharness and pulse oximeter
equipment are low voltage, battery powered, and make no direct electrical connection to mains power.
The pulse oximeter has no electrical contact with the participant. The Zephyr has electrodes which
receive electrical signals from participants but do not pass a current through the participant. All
equipment planned to be used for this proposal conforms to Australian Standard AS/NZ 3551.2005
“Technical management program for medical devices”

4. Possible Benefits

Although we cannot guarantee or promise that you will receive any benefits from this project, a
possible benefit may be the opportunity to trial a new technique that may result in the reduction of
panic symptoms. Another benefit that could result through the CO₂ challenge is that participants may
achieve a de-sensitisation of panic symptoms as a result of repeated exposure through CO₂ inhalation.
The findings and outcomes of this research may also further current understanding of panic disorder
and its treatment.

5. Possible Risks

Whilst the possibility of risks is considered minimal, the CO₂ challenge is likely to elicit panic like
symptoms in participants with panic disorder, which may cause some distress with some individuals.
These sensations are expected to be transient and not harmful. Furthermore, given that the
researcher is a Clinical Psychologist with vast experience in the area of anxiety and panic,
participants will be supported throughout the study.

If you experience concern or distress at any stage of the research there are several ways that you can
get help. The researcher is a Clinical Psychologist and will be available to assist with any concerns
throughout the entire research process. If you would like to discuss any issues that arise with a
confidentiality, you can contact the University of Melbourne by calling 9214 5802. Students and others living in Melbournem may contact the Swinburne Psychology Clinic on 9214 9655 for low-cost community counselling. If you live in Australia, you may also phone Lifeline on 13 11 14, or online at www.depression.net.com.au or www.reachout.com.au

6. Privacy, Confidentiality and Disclosure of Information

Further any information obtained in connection with this project by researchers and that can identify
you will remain confidential. It will only be disclosed with your permission, subject to legal
requirements. The information collected from participants during the research project will be stored on
computer files. Any identifiable information will be removed, and a code applied, once results are
entered into data files. The transcripts will be stored on a computer file which will be password
protected. Following project completion the information collected from participants will be stored on
computer files at Swinburne University and will be password protected. This data will be stored for 5
years following final publication of results. In any publication, information will be provided in such a
way that you cannot be identified. Individual participants will not be identified in any reports of the study, or publications, as only aggregated data will be reported.

7. Results of Project
A summary of the research results will be available for participants who wish to know the outcome of the research. Should participants wish to obtain information on the results of this research, participants can contact the principal researcher who will provide them with a summary.

Data from this study may be used in future journal publications and conferences.

8. Participation is Voluntary
Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you decide to withdraw from this project, please notify a member of the research team.

9. Complaints
This project has been approved by Swinburne's Human Research Ethics Committee (SUHREC) in line with the National Statement on Ethical Conduct in Human Research. If you have any concerns or complaints about the conduct of this project, you can contact:

Research Ethics Officer, Swinburne Research (HERO),
Swinburne University of Technology, P O Box 218, HAWTHORN VIC 3122,
Tel (03) 9214 5218 or +61 3 9214 5218 or research@swin.edu.au

10. Further Information, Queries or Any Problems
If you require further information, wish to withdraw your participation or if you have any problems concerning this project (for example, any side effects), you can contact the principal researcher.

The researchers responsible for this project are:

Prof. David Lilley
Principal Researcher
Swinburne University
Faculty of Art, Health and Design
Hawthorn Campus
Email: d.lilley@swin.edu.au

Prof. Michael Kyriakidis
Associate Researcher
Swinburne University
Faculty of Art, Health and Design
Hawthorn Campus
Email: m.kyriakidis@swin.edu.au

Peter Kyriakidis
Student Researcher
Swinburne University
Faculty of Art, Health and Design
Hawthorn Campus
Ph: 0429 994 168
Email: p.ry4ikidis@swin.edu.au

Prof. Greg Murray
Associate Researcher
Swinburne University
Faculty of Art, Health and Design
Hawthorn Campus
Email: g.murray@swin.edu.au

Dr. Mark Schier
Associate Researcher
Swinburne University
Faculty of Life & Social Sciences
Hawthorn Campus
Ph: 03 9214 8713
Email: m.schier@swin.edu.au
CONSENT FORM: GROUP 1

Project Title: The efficacy of cold facial immersion, apnea and the diving response in the treatment of panic symptoms.

Investigators:
Prof. David Levy (Researcher)
Prof. Michael Kyrios (Researcher)
Prof. Greg Murphy (Researcher)
Dr. Mark Schor (Researcher)
Peter Kyriakoudis (Researcher)

1. I consent to participate in the project named above. I have been provided a copy of the plain language statement to which this consent form relates and any questions I have asked have been answered to my satisfaction.

2. In relation to this project, please circle your response to the following:
   a) I agree to be interviewed by the researcher Yes No
   b) I agree to complete questionnaires asking me about panic cognitions and symptoms Yes No
   c) I agree to participate in the laboratory experiment Yes No
   d) I agree to make myself available for further information if required Yes No

3. I acknowledge that:
   a) my participation is voluntary and that I am free to withdraw from the project at any time without explanation;
   b) the Swinburne project is for the purpose of research and not for profit;
   c) any identifiable information about me which is gathered in the course of and as the result of my participating in this project will be (i) collected and retained for the purpose of this project and (ii) accessed and analysed by the researcher(s) for the purpose of conducting this project;
   d) my anonymity is preserved and I will not be identified in publications or otherwise without my express written consent.

By signing this document I agree to participate in this project.

Name of Participant: .................................................................

Signature & Date: .................................................................

---

Plain Language Statement & Consent Form: Group 1
Version 3 (14/12/16)
Appendix D: Participant Information form and Health Screening
Date: ______________________

Background Information

1. Name: __________________________________________
2. Age (to nearest year): ___ / ___ / ___

3. Sex:  □ Male  □ Female

4. Phone: ________________________________

5. Education

What is the highest degree or level of school you have completed? If currently enrolled, mark the previous grade or highest degree received.

□ No schooling completed
□ Primary school to Year 8
□ Some high school
□ High school graduate – VCE or equivalent
□ Some tertiary education, no degree
□ Trade /technical/vocational training
□ Bachelor’s degree
□ Master’s degree
□ Professional degree
□ Doctorate degree


Are you currently…..?

□ Employed for wages
□ Self-employed
□ Out of work and looking for work
□ Out of work but not currently looking for work
□ A homemaker
□ A student
□ Retired
□ Unable to work

If employed what is your current occupation / title
_____________________________________________________

Comfort with water

How would you rate your perceived level of comfort in water? (Please circle one)

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremely Uncomfortable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Extremely Comfortable</td>
</tr>
</tbody>
</table>
### 7. Health Screening

If female, please indicate if you are pregnant

- [ ] Definitely not pregnant
- [ ] Not sure
- [ ] Definitely pregnant

**Do you have a history of / suffer or have suffered from:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td></td>
<td></td>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A family history of Coronary Heart Disease</td>
<td></td>
<td></td>
<td>Substance abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td></td>
<td></td>
<td>Psychotic symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other chest pain/discomfort</td>
<td></td>
<td></td>
<td>Asthma or other respiratory conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High blood pressure (Hypertension)</td>
<td></td>
<td></td>
<td>Allergies, including latex or rubber</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low blood pressure (Hypotension)</td>
<td></td>
<td></td>
<td>Epilepsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased or high cholesterol</td>
<td></td>
<td></td>
<td>Renal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke, brain haemorrhage or aneurisms</td>
<td></td>
<td></td>
<td>First degree relative with Panic Disorder</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If yes to any of the above please specify:

________________________________________________________________________________________
________________________________________________________________________________________

Do you smoke?  
- [ ] Yes  
- [ ] No  

Do you drink alcohol?  
- [ ] Yes  
- [ ] No

<table>
<thead>
<tr>
<th>How many cigarettes per day</th>
<th>( )</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many glasses per week</td>
<td>( )</td>
</tr>
</tbody>
</table>

Do you ever feel faint, have spells of dizziness or have ever lost consciousness?  
- [ ] Yes  
- [ ] No

Is your doctor currently prescribing you drugs/medication/oral contraceptives?  
- [ ] Yes  
- [ ] No

If yes to drugs/medication/oral contraceptives please specify:

________________________________________________________________________________________
________________________________________________________________________________________

How regularly do you take the above mentioned drugs/medication/oral contraceptives?

Do you know of any other reason why you should not participate in a programme of physical activity?  
- [ ] Yes  
- [ ] No
8. Fitness and Exercise

How many push ups can you do at the moment? ___________

What is your height? _______________(cm)  
What is your current weight? ______________(kg)

How would you rate your current physical fitness compared with others your age? (Circle one answer)

<table>
<thead>
<tr>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
<th>Very Good</th>
<th>Excellent</th>
</tr>
</thead>
</table>

Please let us know the type and amount of physical activity involved in your work:  (Tick one box)

- [ ] I am not in employment (eg. retired, retired for health reasons, unemployed, full-time carer etc.)
- [ ] I spend most of my time at work sitting (such as in an office)
- [ ] I spend most of my time at work standing or walking. However my work does not require much intense physical effort (eg. shop assistant, hairdresser, security guard, childminder etc.)
- [ ] My work involves definite physical effort including handling of heavy objects and use of tools (eg. plumber, electrician, carpenter, cleaner, hospital nurse, gardener, postal delivery workers etc.)
- [ ] My work involves vigorous physical activity including handling of very heavy objects (e.g. scaffolder, construction worker, refuse collector, etc.)

During the last week, how many hours did you spend on each of the following activities? Please answer whether you are in employment or not:

<table>
<thead>
<tr>
<th>Activity</th>
<th>None</th>
<th>Some but &lt; 1 hr</th>
<th>1 hr but &lt; 3 hrs</th>
<th>3 hrs +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical exercise such as swimming, jogging, aerobics, football, tennis, gym, workout, etc.</td>
<td>None</td>
<td>Some but &lt; 1 hr</td>
<td>1 hr but &lt; 3 hrs</td>
<td>3 hrs +</td>
</tr>
<tr>
<td>Cycling (including cycling to work) and during leisure time.</td>
<td>None</td>
<td>Some but &lt; 1 hr</td>
<td>1 hr but &lt; 3 hrs</td>
<td>3 hrs +</td>
</tr>
<tr>
<td>Walking (including walking to work), shopping etc.</td>
<td>None</td>
<td>Some but &lt; 1 hr</td>
<td>1 hr but &lt; 3 hrs</td>
<td>3 hrs +</td>
</tr>
<tr>
<td>Housework or childcare</td>
<td>None</td>
<td>Some but &lt; 1 hr</td>
<td>1 hr but &lt; 3 hrs</td>
<td>3 hrs +</td>
</tr>
<tr>
<td>Gardening or DIY</td>
<td>None</td>
<td>Some but &lt; 1 hr</td>
<td>1 hr but &lt; 3 hrs</td>
<td>3 hrs +</td>
</tr>
</tbody>
</table>

How would you describe your usual walking pace? (Circle one answer)

<table>
<thead>
<tr>
<th>Pace</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow</td>
</tr>
<tr>
<td>Steady average pace</td>
</tr>
<tr>
<td>Brisk pace</td>
</tr>
<tr>
<td>Fast pace (over 6km)</td>
</tr>
</tbody>
</table>
Appendix E: Qualitative Questions
Qualitative Questions

1) What are the challenges you face in managing your anxiety/panic symptoms?

2) What are the challenges you face in managing your anxiety/panic thoughts?

3) How would you describe your experience of cold facial immersion?

4) Describe any changes you experienced in your anxiety/panic symptoms following cold facial immersion?

5) Describe any changes you experienced in your anxiety/panic thoughts following the cold facial immersion?

6) What current strategies do you use to help manage your anxiety/panic symptoms?
   What strategies do you use to manage your thoughts?

7) How could cold facial immersion assist you in managing your anxiety/panic symptoms and thoughts?

8) If you found that CFI assisted you in managing your anxiety/panic symptoms and/or thoughts how likely would you be to practice CFI during a panic attack? Are there any challenges that might prevent you from using CFI?
9) If you found that CFI assisted you in preventing your anxiety/panic, how likely would you be to practice CFI on a regular basis? Are there any challenges that might prevent you from using CFI?

10) If this research was to demonstrate that CFI is an effective intervention in assisting the management of anxiety/panic how would this impact you?

11) What other challenges do you foresee with using CFI to help manage your anxiety/panic?

12) Which of the following methods would you consider using to mimic cold facial immersion and activate the diving response:
   a) ice pack/frozen vegetable packet applied to the face
   b) specially designed waterproof facial mask
   c) splashing cold water to your face
   d) taking up swimming as a sport/exercise
   e) other

13) If the activation of the diving response was to be used as an intervention for managing anxiety symptoms how do you see this developing into an intervention?
Conference Presentations


Publications


Awards

Amplify Ignite Finalist 2018- Excellence in Doctoral Research