Panic disorder

Treatment outcomes and psychophysiological concomitants

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Abstract

Panic disorder (PD) is severe anxiety disorder that follows a chronic course if left untreated. The recurrent panic attacks and persistent worrying of new attacks that are characteristic of PD is highly distressing and can lead to extensive disability. PD is also associated with a malign clinical course, and the physiological changes characteristic of PD, such as altered cardiac regulation is associated with increased risk of somatic illness.

We compared physical exercise (PE) in groups to group cognitive behaviour therapy (CBT) as treatment for PD in a randomised clinical trial (RCT). Thirty six patients with PD with or without agoraphobia were recruited for participation in either PE three times per week or CBT once a week for twelve weeks. Participants were assessed twice prior to treatment initiation. They were thereafter assessed immediate post treatment, and at six and twelve months following treatment termination. We found CBT to yield significantly better long-term effects on the primary outcome measures, though PE still yielded large effects on key measures of panic symptoms and severity, also one year following treatment termination. Importantly, rates for clinically significant change were significantly higher for CBT, and further indicated that the majority of subjects in the PE group had not fully recovered from their disorder.

We also investigated the relationship between vagally mediated heart rate variability (HRV) and cognitive executive functioning in the same sample of patients, and found that these measures were consistently associated. This extends previous research and provides support for the hypothesised relationship between altered functioning in the prefrontal cortex (PFC) and vagally mediated HRV. We also explored the relationships between these measures and clinical variables, and found both cognitive inhibition and HRV to be related to both severity

and duration of the panic disorder. This suggests that cardiac health is related to both cognitive functioning and the clinical state and duration of PD.

Finally, we assessed the same participants on a measure of subjectively reported sleep impairment. We investigated the relationships between this measure and both vagally mediated HRV and scores on cognitive inhibition, and found both sleep onset latency (SOL) and disturbances during sleep to be related to these physiological and cognitive measures. Furthermore, these relationships were independent of level of depression, and the results provide support for the psychobiological inhibition model of insomnia and extend previous findings in support of this model.

List of Publications

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Contents

Abbreviations

PD = Panic disorder

PE = Physical exercise

CBT = Cognitive behaviour therapy

HRV = Heart rate variability

HR = Heart rate

HF = High frequency

CHD = Coronary heart disease

PFC = Prefrontal cortex

CWIT = Color-Word interference test

WCST = Wisconsin card sorting test

D-KEFS = Delis-Kaplan executive function system

PSQI = Pittsburgh sleep quality index

SOL = Sleep onset latency

MI = Mobility inventory

BDI-II = Beck depression inventory II

QoLI = Quality of Life Inventory

SSRI = Selective serotonin reuptake inhibitors

TCA = Tricyclic antidepressants

RCT = Randomised clinical trial

ERP = Event related potentials

SNS = Sympathetic nervous system

PNS = Parasympathetic nervous system

1.0 Introduction

This thesis is an investigation into the treatment of panic disorder. It also aims to elucidate the psychophysiological concomitants of this anxiety disorder, and how these concomitants can be related to the development of the disorder itself and co-morbid disorders, such as sleep disturbance. In the following subsections of this introduction, the background for the current research aims will be presented. Thereafter these aims are delineated, with hypotheses and research questions presented for each study, followed by a description of the methods employed to investigate these. A results-section will summarise the main findings for each study, before these findings and their implications and limitations will be discussed.

The thesis is a synthesis of the three papers upon which it is based, and readers are referred to the reproductions of these papers that are attached for reference and additional details, figures and tables.

1.1 Panic Disorder

Panic disorder (PD) is a severe and prevalent anxiety disorder characterised by spontaneous and recurrent panic attacks. These attacks are experienced as highly distressing, and they are frequently accompanied by beliefs and fears of dying, going mad, fainting, or acting uncontrollably. The physiological symptoms experienced during the attacks are pronounced, and include palpitations, difficulty breathing, feeling suffocated, numbness, tingling sensations, chest pain, sweating, feeling hot and/or cold and a feeling of separation from reality. The marked bodily symptoms are often interpreted as indications of somatic illness, such as a heart attack or suffocation, and many patients seek help at emergency units or are referred for cardiac evaluation during the initial attacks (American Psychiatric Association

[APA], 2000; Dammen, Arnesen, Ekeberg, Husebye, & Friis, 1999; Jonsbu et al., 2009). Furthermore, PD frequently co-occurs with agoraphobia, where patients develop a fear of places and situations in which they feel trapped or cannot easily escape if a panic attack should occur, or where they expect an attack to occur. This co-morbidity can severely disrupt activities of daily life and social functioning (APA, 2000). Estimates of lifetime prevalence rates for PD in the general population range from 3.5-4.7% (Bijl, Ravelli, & van Zessen, 1998; Kessler et al., 2005; Kessler et al., 1994), whereas PD with agoraphobia is reported to have a lifetime prevalence of 1.1-1.5% (Kessler et al., 2006; Kessler et al., 1994). However, prevalence rates for PD are suggested to be substantially higher within clinical populations, such as individuals referred for mental health consultations and heart disease polyclinics, where PD has been estimated to be present in as many as 10% and 60% of patients, respectively (APA, 2000). PD is not only a severe and distressing disorder in itself. It is also the most frequent co-morbid disorder with depression (Roy-Byrne et al., 2000), a combination associated with poorer treatment outcome, more severe functional impairment, more suicide attempts, and greater severity (Roy-Byrne et al., 2000). Even the presence of panic attacks is a risk factor for the development of mental disorders of any kind, and is also associated with greater impairment and help-seeking (Goodwin et al., 2004; Kessler et al., 2006). PD is further characterised by reduced heart rate variability (HRV; Cohen et al., 2000; Klein, Cnaani, Harel, Braun, & Ben-Haim, 1995; Middleton, Ashby, & Robbins, 1994; Yeragani et al., 1990; Yeragani et al., 1993). This is significant, as decreased HRV has been linked to increased risk of all-cause mortality (Jouven, Zureik, Desnos, Guérot, & Ducimetière, 2001; Thayer, Yamamoto, & Brosschot, 2010). Decreased HRV has also been demonstrated to be an independent and strong predictor of mortality following myocardial infarction (Malik et al., 1996). PD is associated with an increased risk of developing coronary heart disease (CHD; Gomez-Caminero, Blumentals, Russo, Brown, & Castilla-Puentes, 2005), and reduced HRV

in these patients has indeed been linked to this increased mortality risk (Alvarenga, Richards, Lambert, & Esler, 2006; Garakani et al., 2009; Habib, 1999; Weissman, Markowitz, Ouellette, Greenwald, & Kahn, 1990). Such somatic consequences related to PD underline the importance of providing treatment to those who suffer from this disorder.

1.2 Treatment of Panic Disorder

Numerous studies have investigated different treatment options for PD, and both psychopharmacological and psychotherapeutic treatment options have been developed. Psychotherapy appears to be most effective (Andrews, Creamer, Crino, Hunt, & Lampe, 2003), and this is also the recommended treatment option (McHugh et al., 2007; McManus, Grey, & Shafran, 2008; National Institute for Health and Clinical Excellence [NICE], 2011). Broadly speaking, it could be said that effective psychotherapeutic treatment models for PD has existed for the last 25 years. Two main models for panic treatment seem to be prevailing. These consist either of Cognitive Therapy for PD according to the model developed by David Clark and colleagues (Clark, 1986; Clark et al., 1994) or the Panic Control Treatment for PD developed by Barlow and colleagues (Barlow, 2002). Both of these treatments are referred to as cognitive behaviour therapy (CBT), and are considered to yield similar treatment responses (Clark et al., 1999; McManus et al., 2008), with remission rates around 80% for patients with PD (Andrews et al., 2003; McManus et al., 2008).

In terms of psychopharmacological approaches, selective serotonin reuptake inhibitors (SSRIs) are the preferred option (NICE, 2011; Pull & Damsa, 2008), providing treatment responses of approximately 60%, depending on the criteria used to determine remission (Pull & Damsa, 2008). Tricyclic antidepressants (TCAs) were the previously preferred psychopharmacological treatment for PD, citing equivalent treatment responses (Pull &

Damsa, 2008). TCAs are however less well tolerated by patients than SSRIs. A caveat concerning pharmacotherapy for PD is the high rates of relapse, regardless of compliance, following such treatment (Simon et al., 2002).

Unfortunately, while manuals for CBT for PD are readily available, it has been documented that as with many other evidence based treatments, CBT for PD is rarely offered to those who suffer from it (Shafran et al., 2009). Psychopharmacological treatment is more readily provided, as this can be administered by the patients' general practitioner. However, with reference to the high relapse rates associated with this treatment, a substantial proportion of patients seeking help for PD would not be cured of their disorder. In addition, psychopharmacological treatment is not acceptable to all patients; neither is CBT nor other forms of psychotherapy. A recent and promising development is the emergence of computerised CBT (CCBT). This paradigm has shown high remission rates (Carlbring et al., 2006), though somewhat lower than what has been found for ordinary face-to-face CBT (Haug, Nordgreen, Öst, & Havik, 2012). Increased availability of this treatment option will hopefully provide CBT more readily to patients suffering from PD.

Based on aforementioned state of affairs, the need to develop additional treatment options for PD seems clearly warranted. Currently, only a relatively small portion of patients receive the recommended treatment for PD (i.e. CBT), and the need to develop a broader range of treatment options is ever important, as not all patients tolerate or benefit from neither CBT nor psychopharmacological treatment.

1.3 Physical Exercise for Panic Disorder

1.3.1 Empirical background

Physical exercise (PE) has long been investigated for the reduction of anxiety. Several cross-sectional studies have shown that physical active people 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), or that they report lower levels of anxiety compared to inactive people (De Moor, Beem, Stubbe, Boomsma, & De Geus, 2006; Harvey, Hotopf, Overland, & Mykletun, 2010). A substantial number of studies have also shown that PE can reduce anxiety levels. However, most of these studies have included healthy volunteers (Long & van Stavel, 1995; Wipfli, Rethorst, & Landers, 2008). It has also been demonstrated that PE can reduce anxiety in subjects with elevated anxiety levels (Petruzzello, Landers, Hatfield, Kubitz, & Salazar, 1991). Fewer studies have investigated the clinically efficacy of PE in reducing anxiety in patients that primarily suffer from an anxiety disorder. Sexton, Mære, and Dahl (1989) found PE to reduce anxiety in a mixed sample of anxious and depressed patients. A more recent study found PE to have a moderate to small treatment effect on generalised anxiety disorder (Herring, Jacob, Suveg, Dishman, & O'Connor, 2012). The perhaps first investigation into the effect of PE on PD was published in 1974 by Orwin. This was a case report, in which situational phobia was treated with the help of physical exertion. Viewed in hindsight, it is not unlikely that the patient in this case report today would have been diagnosed with agoraphobia and PD. Up till recently, only three studies had evaluated the use of PE as treatment for PD. In 1989, Martinsen, Sandvik and Kolbjørnsrud published a study on a mixed sample of inpatients that took part in PE one hour a day for eight weeks in addition to psychodynamic group-treatment three times per week. This treatment led to a significant reduction of symptoms in patients with PD, but symptom

reduction was not found to be significant when the patients were reassessed twelve months later. In 1998, Broocks et al. published results from a randomised clinical trial (RCT) in which patients with PD either received the TCA clomipramine, pill placebo or performed PE. Treatments ran for ten weeks, and participants in the PE-group were requested to complete a 4-mile route at least three times per week, with intensity progressing from walking to running. In addition, participants ran together under supervision once a week. Those authors found PE to be significantly better than placebo, and not significantly different from clomipramine on some primary outcome measures, though they concluded that clomipramine appeared to yield a more rapid effect. In this otherwise well-designed study the authors did not report any long-term effects, nor was the clinical significance of the results assessed. A similar exercise regime was employed in a more recent study by Wedekind et al. (2010). This study compared the SSRI paroxetine with pill placebo, either in combination with PE or relaxation. When PE, together with either placebo or paroxetine was compared against relaxation and either of these additional treatments, no significant differences were found. However, this design, in which both PE and relaxation was administered in combination with pharmacological treatment, challenges the validity and generalisability of these findings on the efficacy of PE for PD. Also, PE plus placebo was found to improve ratings of symptom severity as effectively as paroxetine plus relaxation, and PE plus paroxetine was overall found to yield the largest effects.

It has also been demonstrated that PE can have acute anti-panic effects, reducing the risk of panic attacks in both healthy volunteers (Esquivel, Schruers, Kuipers, & Griez, 2002; Smits, Meuret, Zvolensky, Rosenfield, & Seidel, 2009; Ströhle et al., 2005) and in patients with PD (Esquivel et al., 2008; Ströhle et al., 2009) following a single bout of PE. Furthermore, three RCTs have found that PE reduces anxiety sensitivity (Broman-Fulks, Berman, Rabian, & Webster, 2004; Broman-Fulks & Storey, 2008; Smits, Berry, Tart, &

Powers, 2008) in subjects with increased levels of sensitivity to anxiety and symptoms of anxiety after just 6 sessions of PE performed over 2 weeks time. Anxiety sensitivity seems to precipitate spontaneous panic attacks and is a vulnerability factor for the development of PD (Schmidt, Lerew, & Jackson, 1999).

Thus there appears to be some accumulated evidence to suggest that PE can be a relevant intervention for anxiety, and even more so for PD. What is lacking from the empirical base listed above is a replication and extension of the study by Broocks et al. (1998), where PE can be compared against an evidence-based treatment for PD in which also its long-term effect and the clinical significance of any changes are assessed. The need for PE to be compared against an established psychotherapeutic approach such as CBT has been called for (Broman-Fulks & Storey, 2008), and there has also been a general acknowledgement of the need for more clinically relevant studies in the field of PE as treatment for mental disorders (Lawlor & Hopker, 2001; Salmon, 2001).

1.3.2 Theoretical background for investigating physical exercise for panic disorder

A wide range of different mechanisms have been proposed to explain the effects of PE on mental health and well-being, and a thorough presentation and discussion of these can be found in Buckworth and Dishman (2002) and in Petruzzello et al. (1991). It is however clear that we are far away from a conclusive model that explains the anxiolytic effect of PE (Ströhle, 2009), and the lack of consensus regarding these mechanisms constitute a major obstacle in the utilisation of PE in the treatment of mental illnesses (Scully, Kremer, Meade, Graham, & Dudgeon, 1998). Mechanisms that are related to the concomitants investigated in the current thesis will be presented below, together with mechanisms suggested to be specifically related to PE for PD.

Exposure to bodily sensations (i.e. interoceptive exposure) is one of the mechanisms that has been suggested to explain the efficacy of PE for PD (Smits et al., 2008). This means that patients with PD learn that the physical sensations associated with both anxiety and PE are benign. However, as cited above, an acute bout of PE has also been shown to decrease the risk of panic attacks following challenges such as inhalation of CO_2 or injection of cholecystokinin tetrapeptide (CCK-4) in healthy subjects (Esquivel et al., 2002; Smits et al., 2009; Ströhle et al., 2009) and in patients with PD (Esquivel et al., 2008; Ströhle et al., 2009). One interesting and promising explanation for this acute effect is related to the findings of increased plasma concentrations of atrial natriuretic peptide (ANP) following exercise. It has been shown that an ANP injection reduces anxiety and risk of panic attacks in patients with PD, and furthermore that the anxiolytic effect of exercise correlated with exercise-induced increase in ANP concentrations (Ströhle, Feller, Strasburger, Heinz, & Dimeo, 2006; Ströhle, Kellner, Holsboer, & Wiedemann, 2001). Still, the increase in ANP following exercise has been shown to be highest in untrained subjects (Rogers, Tyce, Bailey, & Bove, 1991), thus the effects of prolonged exercise must be explained by additional mechanisms. Apart from exposure to bodily sensations, several neurotransmitters related to regulation of anxiety have also been found to be sensitive to PE (please consult O'Connor, Raglin, and Martinsen (2000) for a detailed account). Particularly relevant here are the findings that PE leads to increased levels of Gamma-Aminobutyric Acid (GABA) in subcortical brain areas (i.e. corpus striatum; Dishman et al., 1996). This is emphasised here as GABA activity has been related to the regulation of heart rate (HR) and HRV (Friedman, 2007; Thayer, Hansen, Saus-Rose, & Johnsen, 2009), and this will be described more closely in the following section. GABA neurons represent the most widely available inhibitory neurons in the cerebral cortex (Thayer & Lane, 2000), and deficient functioning of the $GABA_A$ receptor in the hippocampus and frontal cortex have been associated with anxiety (Crestani et al., 1999). Although these

findings are based on animal models, the key point here is that the study by Dishman et al. (1996) indicates that the GABAergic system is sensitive to PE.

Another model that is relevant for the concomitants investigated in the current thesis is Solomon's opponent-process model for motivation (Solomon, 1980). This has been suggested as a model for the anxiolytic effects of PE (Petruzzello et al., 1991), and the model posits that the organism (i.e. brain) seeks to maintain homeostasis by counteracting the effects of different external stimuli by an opponent reaction. In the case of PE, the exercise represents an anxiety-provoking stimulus that is counteracted by relaxation. Endorphin release has been suggested as the mechanism behind this descriptive model. However, while some studies have supported this model (Boutcher & Landers, 1988; Petruzzello, Jones, & Tate, 1997), endorphins have largely been disregarded as the mechanism behind mood changes following PE (Buckworth & Dishman, 2002). Other mechanisms have therefore also been related to this model. One proposition has been a change in the balance between the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS), with PE leading to a relative increase in the influence of the PNS over the SNS resulting in net relaxation (Petruzzello et al., 1991). Although the empirical support for this hypothesis has been scant, the emphasis put on a change in balance between the PNS and the SNS is relevant to the theoretical framework underlying the current thesis where HRV is investigated.

Measurement of HRV is a non-invasive method for assessing the influence of the PNS relative to the SNS (Malik et al., 1996), and in line with the above, HRV has been demonstrated to be sensitive to PE. Research on cardiac patients (Coats et al., 1992), young adults with hypertension (Somers, Conway, Johnston, & Sleight, 1991), and healthy adults (Levy et al., 1998) have found HRV to increase following PE. A more recent study found that only four weeks of detraining resulted in a decrease in HRV (Hansen, Johnsen, Sollers, Stenvik, & Thayer, 2004). Furthermore, the previously mentioned fact that HRV is reduced in

patients with PD not only underlines the relevance of this measure with regard to PD and PE, but also strengthens the theoretical rational for expecting PE to be a viable treatment option for PD. This line of thought could be extended to a more recently suggested model for explaining the beneficial effects of PE on mental health. Salmon (2001) argue that this effect can be ascribed to the increased adaptability resulting from PE, an argument that has also been advocated in more recent literature (Ströhle, 2009). HRV has repeatedly been suggested as an index of the individual's flexibility and adaptability (Appelhans & Luecken, 2006; Kashdan & Rottenberg, 2010), and the documented changes in HRV following PE would thus be compatible with this understanding.

1.4 Panic Disorder, HRV and Executive Functioning

The panic attacks experienced by patients with PD have dramatic presentations of autonomic activation. Symptoms such as tachycardia and palpitations have led to the investigation of possible cardiac dysregulation related to PD. In addition to being a risk factor in its own right, decreased HRV has been investigated within a theoretical framework that is relevant for the understanding of developmental and clinical concomitants of PD.

HRV describes the variations in beat-to-beat changes in HR, which is determined by the combined activity of the sympathetic and the parasympathetic nervous system. The innervations of these systems at the sinoatrial node of the heart regulate HR in an antagonistic relationship: A relative increase in sympathetic activity accelerates HR, whereas a relative increase in parasympathetic activity decelerates it. The sympathetic nervous system mediates slower and prolonged increases in HR, while the parasympathetic nervous system exercises the immediate changes in heart rate directly through the vagus nerve (Friedman, 2007). Reduced vagal control of the heart's beats is associated with a reduction in HRV, and the

parasympathetic inhibitory control of the heart through the vagus nerve dominates cardiac control (Levy, 2006). The high frequency (HF) component (i.e. the most rapid changes) of HRV is considered to be an index of the vagal control of the heart (Malik et al., 1996). It has further been suggested that this vagal regulation is controlled by inhibitory neuronal activity in areas of the prefrontal cortex (PFC; Thayer, 2006), and that decreased inhibitory cortical activity is related both to the development of psychopathology as well as decreased HRV (Ahern et al., 2001; Barbas, Saha, Rempel-Clower, & Ghashghaei, 2003; Thayer & Lane, 2007). A comprehensive account of the neurological pathways through which this regulation could take place is presented by Thayer et al. (2009). The key point argued by those authors is that decreased HRV results from decreased inhibitory control from prefrontal areas of the brain, mainly resulting from decreased GABA activity in these areas of the PFC. Importantly, the increase in HR and decrease in vagally mediated HRV seen in anxiety conditions such as PD, can be conceptualised rather as a condition of faulty brakes (i.e. inadequate inhibition) as opposed to a 'sticky accelerator' (i.e. hyperarousal; Friedman, 2007).

The link between vagal cardiac control and activity in areas in the PFC, has been documented both in studies with human subjects (Lane et al., 2009; Ter Horst, 1999) and in animal models (Barbas et al., 2003; Ter Horst, 1999). These relationships have recently been supported in a meta-analysis in which significant associations between neuronal activity in the ventromedial PFC and HRV was found (Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012). The PFC is a part of the brain that has been linked to the so called executive functions (Alvarez & Emory, 2006; Goldman-Rakic, 1998; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004), including working memory, the ability to shift and sustain attention, exert cognitive inhibition, and exercise general mental flexibility (Alvarez & Emory, 2006). It would be expected that reduced activity in the PFC would affect the cognitive abilities related to this brain region (Barbas et al., 2003; Thayer et al., 2009), and

thus that vagally mediated HRV was associated with executive functions. Such a link has been demonstrated in several studies with healthy adults (Hansen et al., 2004; Hansen, Johnsen, & Thayer, 2003; Mathewson et al., 2010), children (Suess, Porges, & Plude, 1994), and infants (Richards & Casey, 1991). It should be noted that Duschek et al. (2009) failed to find support for such association, however the validity of this negative finding has been challenged (Elliot, Payen, Brisswalter, Cury, & Thayer, 2011). More importantly, the directionality of the findings have been consistent, with higher HRV being associated with better performance on measures of executive functioning and vice versa. This association has only to a limited extent been investigated in anxious subjects. Johnsen et al. (2003) assessed a small sample of dental phobics, and found that those with low HRV showed longer latencies in an emotional Stroop paradigm, compared to subjects with high HRV. However, in this study measurements of HRV were collapsed over all four assessments, including baseline, exposure, Stroop assessment, and recovery. As HRV is known to decrease during assessment of executive abilities (Boutcher & Boutcher, 2006; Delaney & Brodie, 2000; Mathewson et al., 2010), it is unclear to what extent these findings reflect a relationship between baseline HRV and executive functioning, and how much they were influenced by performance-related alterations during the Stroop assessment. Thus, the relationship between baseline vagally mediated HRV and executive functioning in anxious subjects is still in need of further inquiry.

1.5 Panic Disorder and Sleep

As described initially, PD and panic attacks are associated with both a malign clinical course, as well as with increased risk of developing co-morbid disorders and conditions. Studies have shown that problems with sleep is common across psychiatric conditions (Okuji et al., 2002), with insomnia being the most commonly reported sleep disorder (Lichstein, Taylor, McCrae,

& Ruiter, 2011). Insomnia refers to complaints of ongoing difficulty falling asleep, staying asleep, waking up too early, or of nonrestorative sleep during the last month. The complaint must cause clinically significant distress or impairment in important areas of life, such as social and occupational. In addition to the sleep complaint, those affected by insomnia report impaired daytime function in spite of adequate opportunity to sleep (Harvey & Spielman, 2011).

Though many models have been developed for explaining insomnia, this disorder has long been considered a disorder of hyperarousal (Perlis, Shaw, Cano, & Espie, 2011). Patients with PD have altered regulation of arousal, and it is therefore not surprising that the characteristics of sleep and prevalence of sleep impairment have been investigated in these patients. Sleep complaints is a diagnostic criteria for some anxiety disorders, such as posttraumatic stress disorder (PTSD) and generalised anxiety disorder (GAD), but not for PD. Nonetheless, studies have shown that approximately 70% of patients with PD report sleep impairments (Mellman & Uhde, 1989; Overbeek, van Diest, Schruers, Kruizinga, & Griez, 2005; Stein, Chartier, & Walker, 1993).

Stein et al. (1993) found patients with PD to report overall impaired sleep quality as measured by the global PSQI score when compared to healthy controls. Patients in that study scored higher (more poorly) than controls on four of the seven subscales of the PSQI: *Sleep quality*, *Sleep latency* (i.e. SOL), *Disturbed sleep*, and *Daytime dysfunction*. As reported previously, PD also frequently co-occurs with depression. Depression is known to be closely associated with sleep disturbances. Still, it has been shown that sleep impairment is a frequent problem for patients with PD, also when patients with co-morbid depression are excluded (Overbeek et al., 2005). As such, it would seem that sleep impairment is an important part of the clinical picture in PD, as well as other anxiety disorders, and a shared underlying

mechanism between insomnia and anxiety has indeed recently been suggested (Uhde et al. 2009).

1.5.1 Sleep and cognitive inhibition

From what has been described above, both PD and insomnia are conditions that have been described by poorly regulated arousal. In the case of PD, and anxiety disorders in general, this increased arousal has more recently been conceptualised rather as a condition with impaired ability to 'de-arouse'. Interestingly inhibition, or lack thereof, has increasingly been implicated as a mechanism for the development and perpetuation of sleep disturbances (Bastien, 2011; Perlis et al., 2011). Several models have been suggested for the development and perpetuation of insomnia. Two key models of insomnia (Perlis et al., 2011), the neurocognitive model of insomnia and the psychobiological inhibition model of insomnia, describes cortical arousal as central to the development and precipitation of insomnia (Borbély, 1982; Espie, 2002; Perlis, Giles, Mendelson, Bootzin, & Wyatt, 1997). One of the main differences between these models is that while the neurocognitive model posits a conditioned state of hyperarousal, the psychobiological inhibition model of insomnia emphasise the failure to inhibit wakefulness (e.g. arousal) as a key mechanism in the development and exacerbation of insomnia. A recent review of the evidence for these two models concluded that both models can account for difficulties in initiating and maintaining sleep (Bastien, 2011). Studies using event related potentials (ERPs) indicate that decreased cognitive inhibition is related to increased SOL (Bastien, St-Jean, Morin, Turcotte, & Carrier, 2008). Furthermore, cognitive events such as rumination, worry and intrusive thoughts are frequently reported by patients suffering from insomnia (Perlis et al., 2011), and such distressing thoughts and perseverative processing are considered central for the development and exacerbation of insomnia (Harvey, 2002). According to Eysenck et al. (2007), anxiety and worry are related to the ability for exercising cognitive inhibition and attentional control.

Thus, it would seem reasonable to expect that aspects of sleep impairment could be related to executive functioning, and more precisely to cognitive inhibition, and that these could also be assessed with other methods than ERP, such as neuropsychological assessment.

However, regarding cognitive impairments related to insomnia, neuropsychological assessments of these have so far mainly yielded inconclusive findings (Shekleton, Rogers, & Rajaratnam, 2010). Shekleton et al. (2010) concluded that the apparent lack of conclusive findings can partly be attributed to heterogeneity in the samples used in the studies that have investigated this. Furthermore, Shekleton et al. (2010) suggest that potential overlap between the clinical group and the control group could have distorted or diluted possible group differences. In addition, they concluded that lack of findings is partly due to the use of measures that lack sufficient sensitivity to detect differences between insomniacs and controls. In this regard they pointed out that the most consistent findings concerned executive functions, and suggested that differences between insomniacs and controls are most likely to be found on sensitive measures of these functions.

How then could the role of neuropsychological characteristics in insomniacs be investigated while circumventing the challenges associated with possibly overlapping or heterogeneous samples? One way to address this could be to investigate sleep impairment in a sample with a high prevalence of sleep disturbances that could also be expected to provide variability on measures of neuropsychological functioning. Patients with PD would be a relevant sample in this regard, as a large proportion of these patients are known to suffer from insomnia. Furthermore, PD is associated with decreased HRV, a measure that has been positively associated with executive functioning. Studies have also indicated that patients with PD have impaired inhibitory control (Dupont, Mollard, & Cottraux, 2000) and executive functioning (Lautenbacher, Spernal, & Krieg, 2002), though results in this area have not been unequivocal (van den Heuvel et al., 2005). Thus, a sample of patients with PD could be

expected to provide variability on both measures of executive functioning and sleep impairment. Cognitive inhibition has been related to sleep impairment both theoretically and empirically, while also being a key executive function. To investigate the relationship between cognitive inhibition and sleep impairment in a sample of patients with PD would thus seem to be a viable approach, and it would also circumvent the challenges described by Shekleton et al. (2010) reiterated above.

1.5.2 Sleep and HRV

The line of reasoning presented above could also adhere to the investigation of a possible association between HRV and sleep impairment. If cognitive inhibition is related to, and important for sleep disturbances, then HRV could also be related to sleep disturbances. Indeed HRV has been found to be related to insomnia (Spiegelhalder et al., 2011), but in line with the concerns raised by (Shekleton et al., 2010), this was only found for insomniacs with objectively determined reductions in sleep. Yang et al. (2011) on the other hand found HRV to be reduced also in patients with insomnia without taking such measures, whereas Bonnet and Arand (1998) found HRV to be reduced in objectively determined insomniacs. Thus, it would seem viable also to investigate the relation between measures of sleep impairment and HRV in a sample of patients with PD, as also here variability on both of these measures would be expected.

2.0 Background and Main Aims

As presented previously, PD is not only a severe disorder with reference to the experienced distress and restriction of movement that is associated with the disorder. It has also high co-morbidity with other disorders such as depression. Patients with PD have also been found to have an altered cardiac regulation, which has been linked to the increased risk of CHD and the increased mortality associated with this disorder. Regarding treatment, several options have been developed, although it appears that the most effective treatment, CBT, is not readily available to these patients. Development of acceptable treatment options is ever important, particularly for a severe disorder such as PD, where spontaneous recovery is known to be rare (Wittchen & Essau, 1993). PE has shown promising results for PD, and calls have been made for this treatment to be compared against a relevant treatment option, such as CBT, that has status as an evidence-based treatment for PD. Furthermore, in previous research on PE for PD, long-term effects as well as clinical significance of changes have not been sufficiently investigated.

HRV has been shown to be a powerful non-invasive measure, and decreased levels of HRV have been associated with an increased risk of malign development in both mental and somatic disorders. It has been documented that HRV levels are linked to measures of executive functioning, but this has not been investigated in the group of patients that has consistently been linked to altered vagally mediated cardiac regulation; patients suffering from PD.

Sleep impairment is known to be prevalent in the patients with PD. These patients are also characterised by decreased vagally mediated HRV, which has been associated with both neuronal inhibition in the PFC and executive functioning. Anxiety has been linked to

impaired executive functioning (Eysenck et al., 2007), and in particular to cognitive inhibition. Studies also suggest that patients with PD have impaired inhibitory ability (Dupont et al., 2000). Failure to inhibit arousal is considered a key mechanism in the psychobiological inhibition model, and cognitive inhibition, as measured by ERPs has been linked to increased SOL. Attentional shifting has also been implicated in sleep impairment (Benitez & Gunstad, 2012), thus two key executive functions have been linked to sleep impairment and symptoms of insomnia. Research on cognitive impairments associated with insomnia has proven elusive, and Shekleton et al. (2010) attributed the lack of conclusive findings in this area to possible clinical overlap between insomniacs and control group. Those authors also emphasised the importance of using measures sufficiently sensitive to impairments in these patients, and further suggested that such impairments would most likely be found on measures of executive abilities. By assessing the relationships between symptoms of sleep impairment and physiological and cognitive measures in a sample of patients with PD, we wanted to circumvent the methodological challenges associated with sample characteristics, as highlighted by Shekleton et al. (2012). This provides the opportunity to investigate the relationship between reports of sleep impairments and symptoms of insomnia in a relevant sample associated with both frequent reports of sleep impairment and physiological and cognitive alterations and variability.

2.1 Research Questions and Hypothesis for Paper I

Research questions:

How does PE compare against CBT in patients with PD, with reference to both short-term and long-term effects, as well as clinically significant change?

Hypotheses:

H1: Based of the effects found in previous studies, we expected CBT to be more effective.

2.2 Research Questions and Hypothesis for Paper II

Research questions:

Is vagally mediated HRV related to executive functioning in patients with PD, and are these psychophysiological measures related to key clinical variables?

Hypothesis:

H1: Based on previous studies, we expected HRV to be positively related to measures of executive functioning.

Due to few and inconsistent previous findings on the relationships between psychophysiological and clinical variables, these associations were assessed exploratory.

2.3 Research Questions for Paper III

Research questions:

Is subjective sleep quality related to cognitive inhibition and vagally mediated HRV in patients with PD?

As these relationships had not been assessed in PD-patients previously and only to a very limited extent in general, we had no pre-specified hypotheses for these research questions.

3.0 Methods

3.1 Issues Overarching the PhD Thesis

Participants in the project were assessed a total of five times (waves). These were at the initial contact (T1), just prior to treatment (pre-treatment; T2), immediately following treatment (post-treatment; T3), at six months follow-up (T4), and at the twelve months follow-up (T5). Outcome measures were assessed on all waves. For theoretical and practical purposes measures of physical fitness, HRV and neuropsychological measures were assessed at T2 and T3. Both T1 and T2 are baseline-assessments, as they were both conducted prior to treatment. As explained in section 3.2.1, the interval between T1 and T2 was related to the recruitment of patients to the RCT, and the outcome assessment at T2 was conducted to monitor clinical stability before treatment initiation. However, in Paper I, T1 is referred to as 'baseline', and T2 is referred to as 'pre-treatment', whereas in Paper II and III T2 is referred to as baseline. Paper I is based on measurements from all T1-5, while Paper II and III primarily investigate measures obtained at T2.

3.1.1 Missing data

Single items missing within inventories amounted to 0.12% of the total number of observations. Total or mean scores on primary and secondary outcome measures across the five waves that were missing due to lacking responses from participants or administrative error amounted to 7.14% of all observations.

3.2 Paper I

3.2.1 Sample and procedure

Individuals between the ages of 18 and 50 years that met the diagnostic criteria for PD with or without agoraphobia according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR; APA, 2000) were recruited. Exclusion criteria comprised the following: Psychotic disorders, substance-abuse, including the habitual use of benzodiazepines, severe major depressive episode, medical conditions that preclude participation in physical exercise, or organic brain disorder. Exclusions according to the first three criteria were established with the Structured Clinical Interview for DSM-IV axis I Disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 1995), whereas the last two criteria were determined through interview with the participant, and when necessary, by consulting with the participant's general practitioner (GP). All participants were also assessed with the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II; First, Spitzer, Gibbon, Williams, & Benjamin, 1994).

The project was implemented within a district psychiatric centre (DPS), and in an aim to recruite a clinically valid and relevant sample for treatment in secondary care, all (n = 60) general practitioners, psychologists and psychiatrists in the centres region were invited to participate in the study by referring relevant patients for treatment in the project. 19 out of 60 of these professionals registered to cooperate with the project. The main primary health care providers cooperating with the DPS were also briefed about the treatment project, and routines for referring subjects for participation were provided. Patients could also be referred from the centres own outpatient clinic as well as from the section for inpatients. However, this all resulted in few referrals, and the majority of participants were eventually recruited through

advertisements in the local press (83%). Recruitment took place from May 2007 till August 2008, and final assessment was completed in January 2010.

The study was conducted within a day-care unit. This unit had a staff of nine, and provided a minimum of 1550 patient-days (days * patients) per year. The unit routinely delivered group treatment primarily for patients referred with a primary diagnosis of anxiety or depression, and CBT and PE were key components in this treatment.

141 people contacted the project, and initial eligibility was established by telephone. Sixty-six potential participants underwent a diagnostic interview on site, and 36 of these were finally randomised to either of the two interventions according to an electronically (http://www.randomizer.org) matched pairwise procedure based on sex and scores on the Beck Anxiety Inventory (BAI; Beck & Steer, 1993). 17 participants were randomised to PE and 19 to CBT.

Participants had a mean age of 37.9 years (*SD* = 8.6), and had suffered from PD for a mean duration of 10.1 years (*SD* = 9.5). More than a third of the sample (38.9%) had previously sought treatment for PD or symptoms of PD. Furthermore, 36.1% used an SSRI, and 13.9% had used benzodiazepines intermittently during the last month. The majority of participants (80.6%) were female and 27.8% reported living alone. Almost half of the sample (47.2%) was in full-time employment six months before inclusion to the study, and 19.4% of participants were in rehabilitation programs, on sick leave or without regular work. Mean Body Mass Index (BMI) was 26.7 (*SD* = 5.8). A majority (80.6%) of participants had agoraphobia, and 38.9% of the sample was depressed. Not counting agoraphobia, participants were diagnosed with a mean of 2.1 additional co-morbid axis-1 disorders and 0.4 axis-2 disorders. All participants were screened for risk-factors related to CHD (i.e. a family history of CHD, hypercholesterolemia, diabetes, hypertension or smoking) in co-operation with a cardiologist, and four participants (11% of the sample) were referred for a cardiac evaluation

before the start of treatment. None of the participants had a history of myocardial infarction or CHD.

No significant differences were found between the participants in the two treatment groups (i.e. CBT and PE) on the characteristics listed above. Neither were they found to differ on any of the outcome measures prior to treatment, nor on the measures of physical fitness or reports on levels of ongoing PE. Bonferroni-corrected within-groups comparisons did not indicate any significant changes from baseline (T1) to pre-treatment (T2) for the participants in the two treatments.

Participants were requested to stabilize use of psychotropic medication during the treatment period and 2 weeks before and after this period, and use of such medication was monitored throughout participation in the study and confirmed via patient self-report. Each participant's use was converted to daily doses, and one-way repeated measures ANOVAs including all five assessments indicated that levels of medication remained stable for participants in both the PE group, $F(2.59, 41.41) = 1.58$, $p = .213$ (Huynh-Feldt correction) and the CBT group, $F(1.70, 30.55) = 0.48$, $p = .593$ (Huynh-Feldt correction).

As the treatments were performed in groups, a sufficient number (twice the maximal group size, i.e. 16) of participants had to be recruited before randomisation and treatment could be implemented for each round. This meant that participants had to wait a variable period depending on the time of their recruitment, with a mean of 68 days for the total sample, before the pre-treatment (T2) assessment and treatment initiation took place. Only one participant dropped out during treatment (from CBT), and one and four participants in the PE group and in the CBT group were not assessed at the 6-month follow-up, respectively. Three participants in both the PE-group and in the CBT-group were not assessed at the 12-month follow-up. Notably, when these follow-up assessments are viewed together, only one and two

participants were not assessed in either of the follow-up assessments for PE and CBT, respectively.

3.2.2 The interventions

The treatments lasted 12 weeks, and were administered in groups of maximum 8 participants. One booster session was offered three months following the end of treatment.

3.2.2.1 Therapists and treatments

PE. PE was supervised by an experienced team of three: one specialized physiotherapist, one occupational therapist, and one psychiatric nurse, and two members of this team were always present during sessions. Sessions were performed three times per week, with three different types of sessions repeated weekly on set days. On these days the PE either focused on i) increasing aerobic fitness through long-distance running (initially walking) and interval training, ii) increasing muscular strength through circuit training, and iii) performing exercises that had varied intensity, including competitive games. Each session lasted approximately 1.5 hours, including introduction, warm up, stretching and debriefing.

PE was administered in accordance with a manual designed at the clinic. This manual was based on recommendations from previous research on PE with anxious subjects (Martinsen, Hoffart, & Solberg, 1989; Meyer & Broocks, 2000; Petruzzello et al., 1991; Stein et al., 1992), and for healthy adults (Haskell et al., 2007; Pollock et al., 1998). A pilot was conducted to ensure the practical and motivational properties of the manual.

In accordance with recommendations (Meyer & Broocks, 2000), participants were briefed initially regarding the physical sensations they might experience during exercises and the similarity of these to symptoms of anxiety. Session attendance was monitored, and participants in PE had a mean attendance rate of 88.7% (*SD* = 10.0) for the treatment sessions. When prohibited from participating in a given session, participants were instructed to perform

an equivalent exercise, and to record this on a provided form. This was however not registered as treatment attendance.

CBT. CBT was supervised by an experienced team of two specialists in clinical psychology with post-graduate qualifications and extensive experience with group treatment. The CBT was administered according to a manual developed by the treatment team. This therapy was based on the treatment model for PD developed by David Clark and colleagues (Clark, 1986; Clark et al., 1994; 1999), and was customized for group sessions. Both therapists were always present during the sessions that lasted approximately 2 hours. Every session also included a brief assessment of symptom severity and evaluation and planning of homework. Sessions were administered once a week, with an attendance rate of 86.0% (*SD* = 23.6), quite comparable to what was reported for PE above.

3.2.2.2 Treatment fidelity

CBT served as the evidence based control condition in the present study, and additional measures were taken to control the quality of this intervention. Six treatment-sessions were therefore randomly selected, evaluated and rated on site by a competent observer (a specialist clinical psychologist that was formally qualified as a supervisor of cognitive therapy by the Norwegian Association for Cognitive Therapy). Quality of the CBT was scored on the Cognitive Therapy Adherence and Competence Scale (CTACS; Barber, Liese, & Abrams, 2003; please refer to section 3.2.3.3 for description), and the random selection of sessions covered half of total treatment content, with sessions drawn from both the initial and final stages of the treatment period. Between sessions, the treatment team received supervision from a different supervisor of cognitive therapy (also qualified by the Norwegian Association for Cognitive Therapy).

CTACS-ratings indicated that both the content and manner of delivery of the CBT was highly satisfactory, with means scores of 4.7, 4.3, and 4.8 for competence, adherence, and overall performance of the therapists, respectively.

3.2.3 Measures

All outcome measures presented below were adapted from English to Norwegian by a translation-back-translation procedure.

3.2.3.1 Primary outcome measures

Agoraphobia. Agoraphobic cognitions and avoidance were measured using the Agoraphobia Cognitions Questionnaire (ACQ; Chambless, Caputo, Bright, & Gallagher, 1984) and the Mobility Inventory (MI; Chambless, Caputo, Jasin, Gracely, & Williams, 1985), respectively. The ACQ is considered to be a measure of fear of fear, and its 14 items that assess the frequency of thoughts common in agoraphobia are all rated on a scale ranging from 1 (*thought never occurs when I am nervous*) to 5 (*thought always occurs when I am nervous*). The Cronbach's alpha for ACQ at baseline in the present study was .75. The MI is a 27-item inventory assessing the frequency of avoidance for different situations relevant to daily life. It is comprised of two subscales that assess avoidance for these situations when subjects are alone and when they are accompanied, and items are rated on scales ranging from 1 (*never avoid*) to 5 (*always avoid*). The subscales of MI are henceforth referred to as MI-Alone and MI-Accompanied, and these subscales provide estimates of the individual's actual freedom of movement, and therein their level of recovery through treatment. As agoraphobics generally feel safer together with a trusted companion, the MI-Alone normally obtains a higher average score than the MI-Accompanied (Chambless et al., 1985). In the present study MI-Alone is part of the criterion for evaluating clinically significant change. Cronbach's alphas at baseline for MI-Alone and MI-Accompanied were .91 and .88, respectively.

Bodily sensitivity. Fear of bodily sensations was measured with the Body Sensations Questionnaire (BSQ; Chambless et al., 1984). This is a 17-item inventory of sensations that can be experienced during anxiety or when in a feared situation. Items are rated on a scale ranging from 1 (*not at all frightened by this sensation*) to 5 (*extremely frightened by this sensation*), and the Cronbach's alpha at baseline for the BSQ in the present study was .87.

Panic Attack Scale. Participants rated panic frequency and panic-related distress and disability on a 5-point scale ranging from 0 (*no panic attacks*) to 4 (*one or more panic attacks per day*) and on a 9-point scale running from 0 (*not at all disturbing*) to 8 (*very disturbing*), respectively. These domains were also rated on an equivalent scale by a clinical psychologist (the first author, AH). This procedure is equivalent to what is described by Clark et al. (1994, 1999).

3.2.3.2 Secondary outcome measures

General anxiety. General anxiety was assessed with the BAI and the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). The BAI consists of 21 items that describe subjective, somatic, or panic-related symptoms. Items are rated on a scale ranging from 0 (*not at all*) to 3 (*severely – I could barely stand it*), and Cronbach's alpha at baseline for the BAI was .89. The STAI comprises two 20-item scales that assess both state and trait levels of anxiety. Subjects rate how much each item applies to them on a scale ranging from 1 (*not at all*) to 4 (*very much*). The STAI-S (state) lists 20 statements referring to the anxiety and tension one experiences at the current moment, while the STAI-T (trait) lists 20 statements regarding the degree of anxiety and tension one feels in general. Cronbach's alpha at baseline for both the STAI-S and the STAI-T was .91.

Depression. Level of depression was assessed using the Beck Depression Inventory II (BDI-II; Beck, Steer, & Brown, 1996). This inventory is comprised of 21 items, and severity

of the different symptoms is rated on a 4-point scale (0-3). The Cronbach's alpha at baseline for the BDI-II was .87.

Quality of life. Participants quality of life was assessed with the Quality of Life Inventory (QoLI; Frisch, Cornell, Villanueva, & Retzlaff, 1992). This inventory assesses 16 different areas of life. Each area is rated on two scales; one for the importance of the particular area to the individual (rated on a 6-point scale ranging from -3 to 3), and one for the individual's level of satisfaction with the area in question (rated on a 3-point scale ranging from 0 to 2). Scores for each area is made up by the product of the scores on these two scales. Areas rated with zero on importance were not included in the overall mean (ranging from -6 to 6). The Cronbach's alpha at baseline for the QoLI was .80.

3.2.3.3 Additional measures

Quality of therapy. Quality of therapy was measured with the CTACS. This is a 21-item rating scale that assesses the quality of cognitive therapy. It covers both adherence to a therapy manual and the competence of therapy delivery. Items are rated from 0 (*poor*) to 6 (*excellent*). A mean score is calculated for each domain, and one item specifically assesses the therapist's overall performance. The Cronbach's alpha across the 6 ratings in the present study was .93 for both the adherence and competence items.

Six-minute walk test. Physical fitness was assessed with the 6-minute walk test (6MWT; Enright, 2003). This is a self-paced measure of sub-maximal functional capacity, where subjects are instructed to walk, and not run, as far as possible within 6 minutes. Assessment in the current study was administered according to guidelines (Crapo et al., 2002), using a corridor of 12.5 meters.

The outcome measures listed in the preceding sections were administered on all five waves; T1-T5, with the exception of the clinician rated version of the Panic Attack Scale that was not rated at 12-month follow-up (T5), as this last follow-up assessment was conducted

via postal mail. Two additional questions were added to this last assessment. These questions pertained to treatment-seeking behaviour and changes in medication with reference to the year following the treatment period. These were phrased in the following manner (here translated into English): 1) 'Have you entered into a new therapeutic treatment directed at your panic disorder following termination of the treatment in the study?' and 2) 'Have you been prescribed new psychotropic medication directed at your panic disorder, or changed your current prescription, following the termination of treatment in the study?'. Participants were prompted to provide additional information if they responded positively to any one of these questions.

3.2.4 Statistical procedures

Group differences on continuous variables were investigated using t-tests for independent samples, and the Fisher's exact test was employed for categorical variables.

Intention-to-treat analyses were used on all outcome measures. Mean or total values that were missing in these analyses were replaced by the last observation carried forward (LOCF). Data were deemed invalid if more than 20% of items for an inventory lacked responses. Mean or total values were in such cases substituted by LOCF.

To reduce the likelihood of a type I error, analyses were performed in two steps. Initially doubly two-way repeated measure MANOVAs were performed on the primary and secondary outcome measures to determine whether the treatments were significantly different over time (Time×Group). If significant differences were found according to this procedure, subsequent two-way (Time×Group) ANOVAs would be conducted on each measure included in the corresponding MANOVA. One MANOVA was performed for each of the following constellation of inventories and rating scales: (1) the inventories MI-Alone, MI-Accompanied, ACQ, and BSQ, (2) self-rated and (3) clinician rated items on the Panic Attack Scales, and (4) all secondary outcome measures. Bonferroni-corrected within-groups effects with reference to

baseline values (T1) were investigated using t-tests, and effect-sizes are reported as Cohen's *d*, calculated using pooled standard deviations (Cohen, 1988).

Reliable and clinically significant changes were investigated as recommended by Jacobson and Truax (1991). Change and recovery was based on changes in panic frequency and scores on the MI–Alone. Thus, a participant had reliable change if change on the MI-alone exceeded the calculated Reliable Change Index. Clinically significant change was assessed with method C as referred to in Jacobson and Truax (1991), where a midpoint between the normal and the clinical population is estimated. Subjects with reliable change, and whose scores fall closer to the mean of the normal population than the clinical population, are considered to have changed clinically significant. However, for a subject to be considered recovered, the additional criterion of having zero panic attacks during the last 2 weeks prior to assessment must also be fulfilled.

3.3 Paper II

3.3.1 Sample

The sample in this study consists of the same participants that are described in section 3.2.1 under Paper I. The current study investigated these participants prior to treatment and randomisation. All measures reported in the current study were obtained at T2 except duration of PD that was assessed at T1.

3.3.2 Procedure

The sample was recruited according to the procedures described for Paper I (please refer to section 3.2.1). As described here, participants waited a mean of 68 days (range: 7-138 days; i.e. from T1 to T2) following the SCID-assessment before HRV and the neuropsychological

and clinical measures in the current study were administered. As described under section 3.2.1, within-groups comparisons indicated that neither of the treatment groups changed significantly from T1 to T2.

Assessments of HRV and neuropsychological measures were conducted on separate occasions and in different clinics. With reference to distance of travel, some participants preferred to complete both assessments on the same day, whereas others conducted the assessments within the timeframe of a few days.

3.3.3 Measures

3.3.3.1 HRV

HRV measures were obtained using a three-lead electrocardiogram (ECG) acquired with an ambulatory monitoring system (VU-AMS; (de Geus, Willemsen, Klaver, & van Doornen, 1995). ECG sampling rate was 1000 Hz, and the Ag/AgCl electrodes (1700 Cleartrace^{TM}, Conmed, Utica, NY) were placed below the right clavicle, 4 cm to the right of the sternum; on the right side between the two lower ribs; and under the left breast, 4 cm below the nipple. The recording session lasted approximately 20 minutes, and was conducted individually in a quiet location with an investigator available. As recommended by Yeragani et al. (1993), ECG was recorded while participants were standing.

Visual QRS-detection was performed with the aid of the ECG QRS scoring utility (version 1.0.5.8; Vrije Universiteit van Amsterdam), and further analyses of the HRV measures were conducted with the Kubios HRV (version 2.0; University of Eastern Finland). In order to ensure a stable and artefact-free recording, the first and last 30 seconds of the five minute recordings were excluded yielding a stable 4-minute recording for each subject. Artefact corrections were kept at a minimum by consulting with the corresponding ECG

signal for each recording. Trend components were removed using the smoothness priors method (Tarvainen, Ranta-Aho, & Karjalainen, 2002) available in the Kubios HRV software.

High frequency (HF) HRV, based on HF-power (ms^2), was used as measure of vagally mediated HRV (Malik et al., 1996). HF-power (ms^2) estimates were derived from an autoregressive algorithm with a standard model order of 16 and a frequency-band of 0.15-0.40 Hz. The root mean squared successive differences (rMSSD) time domain measure and HR were used as secondary cardiac indices. Both HRV measures were transformed to their natural logarithms. As HF HRV and rMSSD were significantly correlated ($r = .90$, $p < .01$), only HF HRV was used to assess the relationships with neuropsychological measures.

3.3.3.2 Neuropsychological measures

The Wisconsin Card Sorting Test (WCST) and The Color-Word Interference Test (CWIT) from the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) were used as measures of executive functioning. Both measures were assessed at a university-based neuropsychological polyclinic by a professional test-technician.

In the current study a computerised version of the WCST; Wisconsin Card Sorting Test: Computer Version 4 research edition (WCST: CV4; Heaton, PAR Staff, & Goldin, 2003) was used. The scoring procedures of this instrument are in accordance with the principles of the original WCST. Still, as recommended the test technician was also familiar with the original version of the WCST. This assessment provided T-scores adjusted for age and education level for *Total errors*, *Perseverative responses* and *Perseverative errors*.

The CWIT consists of four conditions: In *Color naming*, participants name the colours of coloured patches. In *Word reading,* participants read the names of colours printed in black ink. In *Inhibition*, participants name the colour of the ink that the different colour names are printed in when the ink and words are incongruous. In *Switching* (i.e. Inhibition/Switching), participants either read the words when the words are presented in a box or the name of the

colour the words are written in when the box is not present. The first three conditions are equivalent to the original Stroop (Stroop, 1935), and the additional Switching condition is intended to measure cognitive flexibility and complex attentional shifting. The first two conditions are control conditions. Age-adjusted scaled scores, with a mean of 10 and a standard deviation of 3, are provided for all four conditions with regard to the time needed to complete the task. For Inhibition and Switching the test also provides scaled scores for the total number of errors committed. Higher scores indicate better performance.

Both the Stroop and the WCST are considered prototypical measures of cognitive inhibition and attentional shifting, respectively (Myiake et al., 2000). Cognitive inhibition here refers to the definition offered by Myiake et al., and "concerns one's ability to deliberately inhibit dominant, automatic, or prepotent responses when necessary" (2000; pp. 57). Attentional shifting refers to the ability of "shifting back and forth between multiple tasks, operations, or mental sets" (Myiake et al., 2000; pp. 55). In a latent-variable analysis Myiake et al. (2000) found these two executive functions, together with the ability to update and monitor working memory, to constitute key executive functions, underlying other executive functions.

3.3.3.3 Clinical measures

The following clinical measures were used in this study: ACQ, MI, BSQ, BAI, STAI-T, and Chronbach's alphas at T2 for these measures were .72, .91, .85, 91, and .93, respectively. *Panic frequency* and panic-related distress and disability (henceforth referred to as *Panic-related distress*) from the Panic Attack Scale were also assessed. All of the above measures have been described in section 3.2.3.1 and 3.2.3.2 of Paper I. *Panic duration* (i.e. duration of PD) was obtained during the SCID-I assessment at T1.

3.3.4 Statistical procedures

All analyses were conducted using PASW (SPSS) version 17.0. Pearson's *r* was used to investigate correlations and partial correlations between continuous variables. Kendall's tau (τ; Howell, 2012) was used to assess associations that included the Panic frequency and Panic-related distress variables, as these short scales yielded many tied ranks. With reference to the hypothesised directional relationship between HF HRV and the neuropsychological measures of executive functioning, the significance of these questions was assessed with one-tailed tests (Ferguson & Takane, 1989). All other tests were two-tailed.

3.4 Paper III

Sample and procedure is equivalent to Paper II. Please refer to sections 3.3.1. and 3.3.2.

3.4.1 Measures

3.4.1.1 HRV

This measure is described under Paper II. Please refer to section 3.3.3.1. The current study only investigated the primary measure of vagally mediated HRV: HF HRV.

3.4.1.2 Cognitive inhibition

Cognitive inhibition was assessed with the Inhibition condition in the CWIT (henceforth referred to as the Stroop) from the D-KEFS (Delis et al., 2001). Please refer to section 3.3.3.2 under Paper II for descriptions of the D-KEFS, the CWIT, and the Stroop.

3.4.1.3 Measure of sleep impairment

Sleep impairment was assessed with the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). This is a self-report questionnaire that assesses

sleep disturbances and sleep quality during the last month. It comprises 19 items that yield seven component scores: *Sleep quality, Sleep latency, Sleep duration, Habitual sleep efficiency, Sleep disturbances, Use of sleep medication* and *Daytime dysfunction*. The sum of these components yields the global PSQI score. Higher scores indicate poorer sleep, and cut-off for global score above 5 provides maximum sensitivity and specificity for insomnia (Buysse, Ancoli-lsrael, Edinger, Lichstein, & Morin, 2006). Component scores range from 0-3. Cronbach's alpha for the PSQI was .77.

3.4.1.4 Additional clinical measures

The sample was assessed by the following clinical measures: BSQ, ACQ, BAI, STAI-T, BDI-II. Chronbach's alpha's for these measures at T2 were .85, .72, .91, .93. 87, respectively. *Panic frequency* and *Panic-related distress* from the Panic Attack Scale were also used. These measures have all been described in section 3.2.3.1 and 3.2.3.2 under Paper I, and section 3.3.3.3 under Paper II.

3.4.2 Statistical procedures

All analyses were conducted using PASW (SPSS) version 17.0. Pearson's *r* was used to investigate all correlations and partial correlations. Partial correlations (*r*) were used to investigate whether relationships between sleep components and measures of cognitive inhibition and HRV were independent of depression. Thereafter, corrections for multiple comparisons between sleep components and measures of cognitive inhibition and HRV were performed with a modified Bonferroni procedure (Simes, 1986).

3.5 Ethics

All participants in the three studies were required to sign a written informed consent prior to enrolment, and the research project was approved by the Regional Committee for Medical and Health Research Ethics in Western Norway and by the Norwegian Social Science Data Services. The study is registered at ClinicalTrials.gov (identifier: NCT01076777).

4.0 Results

Please refer to the attached corresponding reprints for tables, figures, and additional details.

4.1 Paper I

4.1.1 Between-groups effects

4.1.1.1 Primary outcome measures

The combined analysis of the four inventories (MI-Alone, MI-Accompanied, ACQ, and BSQ) revealed a significant effect of time from baseline to the 12-month follow-up, $F(16, 544) = 7.28$, $p < .01$, as well as a significant Time×Group interaction, $F(16, 544) = 1.71$, $p = .042$. This indicates that the two treatments produced different treatment effects over time as assessed by the primary outcome measures.

The subsequently conducted repeated measures ANOVAs also demonstrated a significant Time×Group effects for the MI-Alone, $F(2.28, 77.61) = 3.75$, $p = .023$, the MI-Accompanied, $F(2.19, 74.28) = 3.93$, $p = .021$, and the BSQ, $F(2.81, 95.43) = 4.08$, $p = .010$, but not for the ACQ.

No significant differences between the interventions were found on the equivalent assessments of panic frequency and panic-related distress and disability, neither on the self-report scales nor on the clinician-rated version. However, both versions revealed a significant effect of time, $F(8, 272) = 15.48$, $p < .01$, and $F(6, 204) = 16.69$, $p < .01$, respectively.

4.1.1.2 Secondary outcome measures

The combined MANOVA performed on the five secondary outcome measures revealed a significant effect of time, $F(20, 540) = 5.21$, $p < .01$, but no significant Time×Group interaction.

4.1.2 Within-groups effects

Bonferroni corrected post-hoc tests demonstrated significant results ($p < .05$) from baseline to the 12-month follow-up on all measures except the QoLI and the STAI-S for CBT. For PE, the equivalent analyses yielded significant results on the following measures: The MI-Alone, the ACQ, the BSQ, both the self-rated- and the clinician-rated versions of panic-related distress and disability, the BAI, and the BDI-II.

4.1.3 Effect sizes

Between-groups effect sizes were generally in favour of CBT, except the effect sizes for the STAI-S, the BDI-II and the QoLI. Within-groups effect sizes for PE were small to moderate on both the MI-Alone and the MI-Accompanied on all assessments following treatment termination. The equivalent assessments were all large on the ACQ and the BSQ. For CBT all effects were large on the corresponding outcome measures. Both treatments produced large effects on panic-related distress and disability following the treatment, although these effects were substantially larger for CBT. Assessments of reduction in panic frequency showed moderate effects for PE and large effects for CBT. Findings on these two latter measures were consistent across the self-report and clinician ratings.

Regarding secondary outcome measures, both interventions yielded large effects on both the BAI and the BDI-II for all assessments following treatment termination. The interventions also yielded moderate to large effects on the STAI-S, and small effects on the

QoLI. The interventions differed on the STAI-T, for which effects were large following CBT, while only moderate after PE.

4.1.4 Reliable and clinically significant change

12 months following treatment termination 63.2% of patients treated by CBT showed reliable improvement and 52.6% had a clinically significant change as measured by the MI-Alone. The equivalent values for PE were 35.3% and 11.8%, respectively. The rates of reliable improvement were not significantly different (p = .181, two-sided Fisher's exact test) across the two treatments, but the difference in rates of clinically significant changes was (p = .014, two-sided Fisher's exact test). Estimated recovery (e.g. freedom from panic attacks and clinically significant change) was 47.4% following CBT and 11.8% for PE (p = .031, two-sided Fisher's exact test).

4.1.5 Treatment-seeking and change in psychotropic medication at 12-month follow-up

Half (50%) of those participating in PE had entered new psychotherapy directed at their panic within 12 months following treatment termination, compared to none in the CBT group (p = .002, two-sided Fisher's exact test). Also, three participants in the PE-group had either increased or been prescribed a new psychotropic medication directed at their panic, compared to one in the CBT group (p = .33, two-sided Fisher's exact test).

4.2 Paper II

Results in this study demonstrated significant correlations (at $p < .05$) between HF HRV and the three subscores of the WCST; Total errors, Perseverative responses, and Perseverative errors, r = .37, r = .35, and r = .34, respectively. HF HRV also correlated significantly with

both time and errors on the Inhibition condition from the CWIT, $r = .30$, $p < .05$, and $r = .43$, $p < .01$, respectively.

Significant associations (at $p < .05$) were found between Panic-related distress and both errors committed on the Inhibition condition and HF HRV, $\tau = .27$, and $\tau = .29$, respectively. Equivalently, Panic duration and both time spent on the Inhibition condition and HF HRV were found to be related, $r = .37$, $p < .05$, and $r = .45$, $p < .01$, respectively.

As found in previous studies (Schwartz, Gibb, & Tran, 1991), HF HRV correlated negatively with age, $r = -.41$, $p < .013$. Partial correlations controlling for age found HF HRV to be significantly correlated with Panic duration also when the participant's age was controlled for, $r = -.34$, $p < .047$.

4.3 Paper III

Two-thirds (69.4%) of the sample had a global PSQI score compatible with the presence of insomnia (i.e. index > 5; Buysse et al., 2006). Depression was found to be positively related to the global PSQI score ($r = .43$, $p = .008$), and the components Sleep disturbances ($r = .41$, $p = .014$), Use of sleep medication ($r = .45$, $p = .005$), and Daytime dysfunction ($r = .48$, $p = .003$). Scaled scores for time and errors on the Stroop were also significantly but inversely related to the global PSQI score, $r = -.35$, $p = .037$ and $r = -.35$, $p = .041$, respectively. Furthermore, these correlations were also significant after controlling for the level of depression, $r = -.36$, $p = .036$ and $r = -.39$, $p = .019$, respectively. Regarding the different components of the PSQI, both scaled scores for time and errors on the Stroop were inversely related to scores on both Sleep quality, $r = -.34$, $p = .041$ and $r = -.37$, $p = .027$, respectively, and Sleep latency, $r = -.40$, $p = .017$ and $r = -.41$, $p = .013$, respectively. Both errors on the Stroop and HF HRV correlated significantly and negatively with Sleep disturbances, $r = -.37$,

p = .027, and r = -.43, p = .008, respectively. Also these relationships retained significance following control for the level of depression, r = -.41, p = .015 and r = -.43, p = .010, respectively. However, after controlling for multiple comparisons using the Simes procedure, cognitive inhibition was no longer significantly associated with the global PSQI score and Sleep quality.

5.0 Discussion

5.1 Main Findings

5.1.1 Physical exercise for panic disorder

We found that CBT was significantly better than PE over time as assessed in the combined analysis of the four primary outcome inventories. Although analyses of the other primary and secondary outcome-measures indicated no difference between the treatments over time, effects following CBT were almost exclusively larger than the effects from PE, and CBT also yielded a larger proportion of significant changes from baseline to any of the assessments following treatment. These findings are corroborated by the differences in clinically significant change and treatment seeking behaviour within one year after treatment.

The effects found for PE in the current study are not surprising with reference to the study by Broocks et al. (1998), where PE was also found to yield large post-treatment effects. The important contribution of the current study is the demonstration that this effect is also present one year following treatment termination. Furthermore, the current study also indicates that such changes following PE are not necessarily sufficient to provide clinically significant changes or remission from PD. Regarding CBT, it had already been demonstrated that treatment effects were retained for at least a year (Clark et al., 1994; 1999). None of the previous randomised studies on PE for PD included long-term follow-up (Broocks et al., 1998; Wedekind et al., 2010), but the current results are at odds with the findings in the naturalistic study by Martinsen et al. (1989), where the changes for patients with PD were non-significant at the one year follow-up. Although CBT generally yielded larger and more consistent effects, the effects following from PE were large. The finding that these changes

persist, or continue, over the next year is noteworthy, especially as subjects were not specifically instructed to continue PE after treatment.

Among the primary outcome inventories, effects from PE were smallest on the measure assessing agoraphobic avoidance (MI), and it could be argued that the assessment of clinically significant effects was rigged in the favour of CBT. CBT for PD is directly targeted at cognitive misinterpretations of bodily symptoms, and at challenging the patient's thoughts and conclusion regarding these. However, CBT also works directly on agoraphobic avoidance, and subjects are directed to challenge their own expectations and their fear during in vivo exposures. This exposure mainly takes place as homework between sessions, but when necessary, by use of guided in-situ exposure. This was also the case in the current study. PE, on the other hand, does not have this element of directed guidance towards exposure. Still, the gold standard for assessing clinically significant change for PD are the ones pertained to in the current study (Baillie & Rapee, 2004), and this also makes sense from a clinical perspective. In order to be cured of PD one must both be free from panic attacks, as well as have improved substantially in terms of freedom of movement. When considering the changes resulting from PE, it appears that large changes had taken place in subjects regarding both the interpretation of bodily symptoms, and cognitions on agoraphobic fear. However, without the element of guided exposure, these changes in thought did not appear to manifest themselves into changes in overt behaviour. Thus, PE alone does not appear to be a sufficient treatment for PD, contrary to what has been suggested (Asmundson et al., in press; Otto et al., 2007; Smits, Powers, Berry, & Otto, 2007).

5.1.2 Panic disorder, HRV and executive functioning

The current study demonstrated that key executive functions were related to vagally mediated HRV. The results also indicated that measures of panic severity and duration can be related to both measures of executive functioning and vagally mediated HRV. Based on previous

research on healthy subjects (Hansen et al., 2004; Hansen et al., 2003; Mathewson et al., 2010; Richards & Casey, 1991; Suess et al., 1994) and the study on dental phobics (Johnsen et al., 2003), we expected to find a positive relationship between the executive measures and HRV. These findings were here consistent and selective, and there was no significant relationship between the non-executive control conditions Word reading and Color naming. The lack of association between the Switching condition and HRV was not expected, however. According to Delis et al. (2001) Switching is a measure of attentional shifting, supposedly requiring the ability for set shifting in addition to cognitive inhibition, and Delis et al. (2001) cite significant associations between this condition and perseverative errors on the WCST. However, according to Lippa and Davis (2010), Switching could in fact be less demanding, due to the increased proportion of word reading in this condition. They further found this to be particularly relevant for young subjects, a characteristic that could have relevance for a substantial proportion of the current sample. As such, it is possible that the Switching condition was not sufficiently demanding to require an executive ability related to vagally mediated HRV in the current sample.

The immediate implications of the current findings are that baseline or resting levels of vagally mediated HRV are related to executive functioning across a broad spectrum of conditions, from healthy to anxious subjects. It is also important that HRV was assessed at baseline, and is thus independent of possible cardiac responses elicited by the neuropsychological assessment itself. This means that the current associations reflect a tonic HRV state in these patients, and provides support for the hypothesised relationship between vagally mediated HRV and activity in areas in the PFC (Thayer et al., 2012). As executive functions, and especially those assessed here, are related to cognitive flexibility (Rossi et al., 1997), this furthers the case for those suggesting HRV to be a non-invasive marker of flexible functioning (Appelhans & Luecken, 2006; Kashdan & Rottenberg, 2010; Thayer & Friedman,

2002). It also implies that both mental health and cognitive functioning are related to cardiac regulation and cardiac health.

The associations found between clinical variables and both HRV and executive measures are interesting, although they should be treated with caution due to the exploratory nature of these results. The findings do however replicate and extend previous findings. Both HRV and cognitive inhibition were found to be negatively associated with measures of PD severity. Cognitive inhibition has been found to be negatively associated with anxiety (Eysenck et al., 2007), or impaired in the presence of PD (Dupont et al., 2000). Thus the negative association found here between cognitive inhibition and Panic-related distress is compatible with those previous findings, and indicates that cognitive inhibition is also related to experienced severity of PD. As PD is characterised by decreased HRV, it could also be expected that HRV is associated with PD severity (i.e. Panic-related distress). Nonetheless, previous assessments in this area have been both scant and inconclusive (Alvarenga et al., 2006; Yeragani et al., 1990; Yeragani et al., 1993), and the current findings suggest that this should be further investigated. We also found Panic duration to be related to both HRV and cognitive inhibition. The question that naturally arises is whether longer duration of PD leads to decreased HRV and relatively impaired cognitive inhibition, or vice versa. This is further discussed under section 5.2 Psychophysiology in Panic Disorder.

5.1.3 Panic disorder, inhibition and sleep

The current study found cognitive inhibition to be related to key constructs regarding the development and persistence of insomnia and sleep impairment (Espie, 2002; Perlis et al., 1997). This supports the psychobiological inhibition model of insomnia (Borbély, 1982; Espie, 2002), and extends previous findings on the relation between cognitive inhibition and sleep impairment (Bastien, 2011; Bastien et al., 2008). Bastien et al. (2008) found ERPs measuring cognitive inhibition to be related to sleep onset latency. The current study found a

different measure of cognitive inhibition (i.e. results on the Stroop) to be related to both sleep initiation (Sleep latency) and sleep maintenance (Sleep disturbances). Importantly, the current findings were independent of level of depression.

HRV was also found to be related to Sleep disturbances. This could mean that HRV reflects neuronal inhibition in the PFC that can be related to sleep impairment. Still, the interpretation of this finding is somewhat less straightforward. Sleep disturbances was the only sleep component that HRV was found to be related to, and even though this relationship was strong, the result regarding the relationship between HRV and the different components of the PSQI is overall less consistent than what was found for cognitive inhibition. Furthermore, there is a likely alternative explanation for this relationship. Stein et al. (1993) found patients with PD to differ from controls on Sleep disturbances. As Sleep disturbances is a multifaceted component comprising a variety of disturbances, those authors explored which disturbance patients with PD and controls differed on. They found patients with PD to report significantly more disturbances on the item 'Cannot breathe comfortably'. It should here be noted that some measures of HRV are known to be related to subjects' breathing frequencies. However, it has recently been shown that the method for assessing vagally mediated HRV utilised in the present study is a robust measure against respiratory influence (Lewis et al., 2012). Thus, it is unlikely that the relationship between the current HRV measure and Sleep disturbances was mediated primarily by subjects' breathing pattern. However, nightly panic attacks is a characteristic feature of PD (APA, 2000), and the relationship in question could reflect the relatively decreased HRV found in patients suffering from such nocturnal panic attacks (Sloan et al., 1999). This means that patients with nightly panic attacks report more disturbances during sleep, while these same patients also have relatively reduced HRV compared to patients that do not experience these nightly attacks.

Yang et al. (2011) found an association between HRV and the global PSQI score in depressed patients, but not in insomniacs. In the current study we did not find a significant association between the global PSQI score and vagally mediated HRV. The current findings thus add to the literature regarding HRV and subjectively reported sleep impairment within different group of patients.

5.2 Psychophysiology in Panic Disorder

In addition to evaluate the clinical properties of PE as treatment for PD, the current thesis aimed to elucidate the psychophysiology in these patients. Patients with PD are known to have altered physiological regulation in terms of impaired vagally mediated cardiac control. As presented in section 1.4, it has been suggested that decreased vagally mediated HRV reflects reduced neuronal inhibitory activity in areas in the PFC associated with executive functioning. Furthermore, it has been established that the heart and these areas in the PFC are linked anatomically, and that activity in these areas is related to vagally mediated HRV. Studies have also shown that vagally mediated HRV is related to executive functioning in healthy subjects. Such a relationship had however not been previously documented in patients with PD, the group of anxiety patients most consistently characterised by decreased vagally mediated HRV.

5.2.1 Psychophysiology and the development of panic disorder

Thayer et al. (2009) have suggested that decreased HRV constitutes a vulnerability for the development of psychopathology, due to the associated altered functioning of the PFC. Furthermore, when the state of anxiety has developed in the individual, these cognitive and physiological changes perpetuate the clinical condition due to the impact the decreased cognitive flexibility has on reasoning, functioning and appraisal of situations and stimuli

(Brosschot, Gerin, & Thayer, 2006; Friedman, 2007; Thayer & Friedman, 2002; Thayer & Lane, 2000). The current findings indicated that both duration of the disorder, and the distress experienced from it were related to both of the investigated domains of psychophysiology; executive functioning and vagally mediated HRV. As mentioned in section 5.1.2, the results from the study in the current thesis can only indicate that there is a relation between the variables in question. However, the directionality and clinical relevance of these findings regarding the development and persistence of PD could be more evident when these findings are considered together with previous studies and theoretical developments.

The altered functioning in the PFC is thought to result from experienced stress (Thayer et al., 2009). This is further suggested to lead to a concomitant decrease in vagally mediated HRV and changes in executive functions related to this part of the brain. Stressful life events are linked to the development of PD (APA, 2000). The questions are thus: Do stressful life events lead to reduced inhibitory activity in the PFC with concomitant decreased in vagally mediated HRV and altered executive functioning that increase the risk for the development of psychopathology like anxiety, or does such stress might result in anxiety which can then lead to the described physiological and cognitive changes? Melzig et al. (2009) found decreased HRV to result in increased startle potentiation for both healthy subjects and subjects with PD. Those authors even suggested that decreased HRV could be an endophenotype for the development of certain anxiety disorders. HRV has in the current thesis been demonstrated to be positively related to executive functioning also in patients with PD, and this relationship is known to exist also for a variety of different groups of healthy adults as well as children. According to Brosschot et al. (2006) it is the perseverative cognitive processing that reinforces the impacts of events on the individual. The results by Melzig et al. (2009) suggest that subjects with decreased HRV have increased apprehensive worry, and as vagally mediated HRV is positively associated with cognitive flexibility, these results appear to be in

line with Brosschot et al. (2006). Thus, the current relationship between Panic-related distress and both HRV and cognitive inhibition could be interpreted to indicate that level of distress is affected by these cognitive and physiological changes. This perspective can be complimented by the theoretical suggestions by Eysenck et al. (2007), who argue that the state of anxiety alters the executive functioning, and specifically the two executive functions addressed in the current thesis. These cognitive changes lead to the preferential processing of threat related stimuli, either internal or external in anxious subjects, and to a continuous search for threats when in the presence of neutral stimuli, either internal or external. When considering PD, this pattern seems compatible with the clinical presentation of this disorder, where patients are known to persistently monitor themselves for changes in body sensations or the avoidance of potentially threatening situations (i.e. where they can experience a panic attack). Thus, the altered executive functioning perpetuates and reinforces the appraisal of threat by the anxious individual so that the stressful state of anxiety persists, thereby sustaining the reduced inhibitory functioning in the PFC and the vicious cycle that renders anxiety a steady state.

As argued by Brosschot et al. (2006) perseverative cognitions mediate the transition from brief or temporary stress into a prolonged state of stress and possibly psychopathology. Based on this, it also seems most likely that the altered psychophysiology, as measures here, mediates prolonged duration of PD and not vice versa. As such, the associations found between psychophysiological and clinical variables in the current thesis can be interpreted within the presented theoretical notions and previous findings. They also extend previous findings by indicating that clinical developmental factors are related to these important psychophysiological variables. It should nonetheless be stressed that the current findings are exploratory and cross-sectional, and that these findings can merely highlight these issues and generate hypotheses as those presented above. More rigorous studies are needed to determine the directionality, and certainty of these relationships.

5.2.2 Psychophysiology and sleep in patients with panic disorder

According to the psychobiological inhibition model, hyper-arousal in insomnia follows from impaired ability to inhibit wakefulness (i.e. arousal). As described in section 1.5.1, studies using ERPs have found cognitive inhibition to be related to key domains of sleep impairment. Anxiety, including PD, has been closely related to sleep impairment and insomnia. Insomnia is a highly frequent co-morbidity to PD, and anxiety disorders have both been suggested to share underlying characteristics with sleep disorders, and to precede the development of sleep impairment. If PD and anxiety are related to cognitive and physiological flexibility, it would be relevant to know how these constructs relate to a frequently co-occurring and possibly related co-morbidity such as sleep impairment.

The relationships between cognitive inhibition and sleep initiation and maintenance found in the current study can be interpreted in at least two ways: Cognitive inhibition is related to anxiety and worry (Eysenck et al., 2007). Worry either directly increases sleep latency and awakenings, or leads to increased arousal with the same consequences. Alternatively, cognitive inhibition is related to the ability to de-arouse, which is posited to be one of the main developmental and perpetuating mechanisms in insomnia and sleep impairment (Espie, 2002). Both of these explanations suggest a temporal developmental relationship between inhibitory control and sleep impairment. However, according to the first explanation, the relationship between cognitive inhibition and sleep is mediated by the development of anxiety. The developmental interrelations between anxiety, depression and insomnia are still a topic for discussion. However, studies have shown that the pervasive developmental pattern can be described to evolve from anxiety to insomnia and from insomnia to depression (Johnson et al., 2006; Ohayon and Roth, 2003). As anxiety is associated with impaired cognitive inhibition, and anxiety is considered to precede insomnia, this suggests that impaired cognitive inhibition could be an antecedent to the development of

sleep impairments and insomnia. As delineated above, this would also be in line with the psychobiological model of insomnia.

Previous research has found that impairment of inhibitory ability persists in depressed patients, irrespective of changes in level of depression (Årdal and Hammar, 2011; Biringer et al., 2007; Hammar et al., 2010). Equivalent results have been reported regarding insomnia and depression, where patients have been found to have residual sleep problems following remission from depression (Carney et al., 2007; Manber et al., 2003). Such residual sleep problems have even been found to be a predictor for repeated depression (Ohayon and Roth, 2003; Reynolds et al., 1997). Persistence of sleep impairment and impaired cognitive inhibition following remission from depression could have many explanations. The perhaps most immediate suggestion pertains to the mentioned chronological interrelationship between anxiety, sleep impairment and depression. Thus, when depression is cured, anxiety, impaired cognitive inhibition, and also insomnia persist. Based on the current results and the argument presented above it could be suggested that the co-occurrence of persistent cognitive impairment and persistent sleep problems following remission from depression could be two sides of the same coin. Thus, the psychophysiological changes associated with PD addressed here can be related to developmental and perpetuating factors for insomnia and sleep impairments which frequently co-occur with PD.

5.2.3 Psychophysiology and treatment effect of physical exercise for patients with panic disorder

Previous knowledge on psychophysiology in these patients, and the sensitivity of measures of psychophysiology for PE provided an important part of the theoretical platform upon which the rational for providing PE as treatment for these patients was based.

Both the current and cited previous findings indicate that PD is a severe anxiety disorder, characterised by alterations in behaviour, cognitive and physiological functioning, and mortality risk. Furthermore, these cognitive, and possibly also physiological, changes are related to frequently occurring co-morbidities found in PD (i.e. sleep). Psychotherapy has been found to result in increased HRV, thus possibly being cardioprotective for these patients (Friedman, 2007). The current findings both show that vagally mediated HRV is related to executive functioning in patients with PD, and that PE can provide a substantial and lasting reduction in key symptoms of PD. As described initially, the mechanisms behind the anxiolytic effects of PE are still not conclusively known. However, two different accounts of the clinical changes resulting from PE can be related to the mechanisms investigated here. In line with Solomon's opponent-process model for motivation (Solomon, 1980), it has been suggested that the sympathetic activation accompanying PE leads to the opponent reaction of increased parasympathetic activation following exercise. Vagally mediated HRV is an index of parasympathetic activity, and HRV has been found to increase following PE (Coats et al., 1992; Levy et al., 1998; Somers et al., 1991). Vagally mediated HRV is considered a measure of the organism's adaptability (Appelhans & Luecken, 2006; Kashdan & Rottenberg, 2010), with reference to its close link with the PNS and cardiac regulation, as well as through the association with executive functioning. It is therefore interesting and noteworthy that research on the acute effects of PE indicates that this can result in increased mental flexibility as indexed by cognitive inhibition (Chang & Etnier, 2009), and that habitual exercise leads to improved executive functioning in both adults and older adults (Colcombe & Kramer, 2003; Smith et al., 2010). Furthermore, Hansen et al. (2004) found that abstaining from PE leads to both a decrease in executive functioning and decrease in vagally mediated HRV. This line of reasoning concurs with Salmon (2001), who argues that the beneficial effects of PE on mental health results from the organisms' increased adaptability.

As described in sections 1.3.1 and 1.3.2, the anxiolytic effects of PE have also been related to reduced fear of bodily sensations resulting from the exposure for these symptoms and sensations during PE. Fear of bodily sensations is a key construct in the cognitive model of panic (Clark, 1986; Salkovskis, Clark, & Hackmann, 1991). PE has also been found to reduce anxiety sensitivity effectively, and this construct has been shown to be an important predictor for the development of PD (Schmidt et al., 1999). However, according to the discussion above, the mechanisms behind the anxiolytic effect of PE could be discussed and investigated at a more fundamental level.

As PE appears to impact both cognitive and physiological flexibility, this intervention could facilitate clinical change indirectly through increased flexibility in these domains. In terms of cognitive flexibility such change could reduce the perseverative processing of threats and thus reduce the impacts of events on patients with PD. This could in turn lead to reduced distress and more cognitive resources available for daily functioning and reappraisal of situations and stimuli. PE could thus act indirectly on the level of anxiety and symptoms by breaking the viscous perpetuating circle of this disorder. Accordingly, PE, regardless of other anxiolytic effects, could possibly act on the anxious individual through increased psychophysiological changeability and adaptability. This would be expected to result in decreased anxiety in its own right. However, it would also seem plausible that the amount of clinical change following treatment with PE would be partly determined by what other therapeutic steps made by the individual. In the current treatment study we found PE to lead to large reduction in symptoms, and in particular on appraisal of bodily sensations and agoraphobic cognitions (i.e. fear of fear). The differences between the two treatments were largest in terms of changes in overt behaviour, as measured by mobility in everyday situations. This indicates that while cognitions relating to panic and anxiety were reduced following PE, this did not necessarily lead to increased exposure to such situations to the

extent seen following CBT where this is targeted directly. According to this line of reasoning, PE could be an important adjunct to other interventions for PD and anxiety, and pilot studies have indicated that such a combination can be acceptable to patients (Cromarty, Robinson, Callcott, & Freeston, 2004; Merom et al., 2008).

5.3 Methodological Issues

5.3.1 Validity

The question whether the current findings can be generalised to the global population is paramount when interpreting the findings of a given study. The three studies reported upon in the current thesis have all investigated the same sample; the subjects recruited for participation in the RCT.

As the current study was implemented within a district psychiatric centre (DPS), it was desirable to be able to treat patients with PD that were naturally referred to the centre. Furthermore, this was the first comparison of PE against an evidence-based intervention, thus if PE had proven to be a recommendable treatment option, it was important that it was valid for patients referred for treatment within secondary care for psychiatric disorders. As described in section 3.2.1, the majority of patients were eventually recruited via the local press. This could be a threat to the generalisability of the current results to the populations found in district psychiatric centres. However, participants in the current sample had on average suffered from PD for a mean of 10 years, and this is comparable to what has been found in clinical populations in other district psychiatric centres in the area (Nordgreen, Haug, Öst, Heiervang, & Havik, 2011). It should be noted that the duration of illness in the current study is substantially longer than what has been reported for the samples in the studies by Broocks et al. (1998) and Clark et al. (1994; 1999), where participants had suffered from PD

for approximately three years. This is not surprising, as all three studies above recruited a more selected sample than what was the case for the present study. Most notably, participants in those studies were required to report panic attacks within the last two weeks before inclusion. We chose to omit this criterion with reference to clinical validity as frequency of panic attacks is known to vary widely, and patients with PD can be free from panic attacks for extended periods (APA, 2000). Longer duration of illness has been associated with poorer treatment response (Chavira et al., 2009). This is perhaps not surprising, as a more chronic sample would be less likely to show spontaneous recovery, even though spontaneous recovery is known to be relative infrequent in PD (Wittchen & Essau, 1993). Considering this, and the notion that the current study included a less selected sample, it should come as no surprise that the current study reported somewhat smaller effects for both interventions, and lower treatment response to CBT compared to the studies by Broocks et al. (1998) and Clark et al. (1994; 1999). However, based on what has been said above, it is possible that the current findings represent a more valid estimate of the size of effects that can be expected when treating patients with PD with PE or CBT within this clinical setting.

However, other characteristics of the current sample could influence the interpretation of the findings in this thesis. The current sample showed a clear female preponderance. PD is known to be at least twice as prevalent in females, whereas more than 80% of the participants in the current sample were female. The number of males was too low for allowing investigation of gender differences in treatment effect, thus it is not known whether the current results can be applied with more certainty to females than males. This means that the results reported in the current thesis should be treated with caution regarding the generalisation to the community. This is particularly true regarding the results including HRV, as this measure is known to show different values for males and females as well as across age (Agelink et al., 2001). The relationship between HRV and Panic duration was

controlled for the influence of age, but a more fine grained analysis of sub-groups was not possible with the current sample size. Therefore, the findings related to HRV are primarily applicable to females in the same age as those in the current study.

5.3.2 Power

Due to a lack of previous studies that had compared PE to psychotherapy, the power-analysis that proceeded inclusion and recruitment to the RCT in the current thesis was based on previous findings from single studies that had either compared CBT to a tricyclic antidepressant, (imipramine; Clark et al., 1994) or PE to a comparable[1] tricyclic antidepressant (clomipramine; Broocks et al., 1998). Though these two studies were comparable in many respects, they did not employ directly comparable outcome measures. However, they both reported results on composite measures that comprised assessments of avoidance, fear of fear as well as ratings of panic severity and frequency. Thus, the current power-analysis was based on the relative differences between the two active treatments and the control condition at post-treatment. Broocks el al. (1998) found no significant differences between the two active treatments, whereas there were large differences between the CBT and imipramine following treatment in the study by Clark et al. (1994). We therefore expected a difference between the two treatments at post-treatment of at least 1.0, and with reference to the studies by Clark et al. (1994; 1999) this effect was expected to endure following CBT, whereas for PE it was possible that this effect would decay over time (Martinsen, Sandvik, et al., 1989). From a conservative perspective, we set the expected effect to be 0.9. We used and allocation ratio of 1, alpha level of .05, a power of .80 (one-tailed), and conducted the analysis with the G*Power software (Faul, Erdfelder, Lang, & Buchner, 2007). This indicated that a sample of 16 participants in each group would be sufficient.

[1] It should be noted that these two antidepressants have been shown to yield somewhat different effects for PD (Modigh, Westberg, & Eriksson, 1992).

However, as described above, we included a more chronic sample than what had been investigated in the studies referred to above. We also had fewer exclusion criteria for participation than in those studies, and this could have resulted in a less homogenous sample. Such increased variability within the sample could dilute treatment effects and demand a larger sample to detect possible differences between the treatments. Also, as described above, the power analysis was based on composite measures. Not all measures are equally sensitive to change, thus it is possible that some non-significant findings could have become significant with a larger sample. However, as an RCT compares two treatments in which one is expected to yield better effects than the other, overshooting the estimated sample required is not unproblematic from an ethical perspective.

The issue of power is also relevant regarding the two baseline studies. From what has been described above, it is evident that the sample size was determined based on the treatment effects expected in the RCT. Both of the baseline studies reported large effect sizes that were in line with expectations, though not all of these were significant. This was most notable for the relationships between attentional shifting and the psychophysiological variables, that were all large, but not significant. Equivalently, the relationships between sleep quality and cognitive inhibition were both consistent and of large magnitude. They were however not all significant, despite these large effect sizes.

5.3.3 Other methodological issues

Apart from the methodological issues described regarding power and validity, other methodological challenges, obvious with the bias of hindsight, have become apparent. These are described below.

As we compared PE to another intervention in the RCT, it would have been useful to be able to document an improvement in physical condition following the treatment period. We opted for the sub-maximal assessment in the 6MWT. However, a more reliable

manipulation check such as assessment of VO_{2max} could have been preferred. Assessment of VO_{2max} is the gold standard for testing of physical capacity. Still, when the study was planned, previous studies and recommendations indicated that improved physical fitness was not necessary for anxiety reduction (Martinsen, Hoffart, et al., 1989; Meyer & Broocks, 2000). Furthermore, assessment of maximal capacity requires an intensive bout of PE. Based on the findings that an acute bout of PE can be panicogenic for patients with PD (Esquivel et al., 2008; Ströhle et al., 2009), we were worried that such testing could amount to an intervention in its own right. The current PE-treatment was intended to be implementable within secondary mental health care, where assessment of VO_{2max} would not be readily available. Performing this assessment could thus reduce the validity of possible findings on PE for these settings. There are also submaximal methods for estimating VO_2 capacity, but these also require physical exercise of a fairly high intensity, something that would be aversive to a substantial proportion of patients prior to treatment. We therefore decided to use a less demanding submaximal assessment, where the participants could choose the physical output that they were comfortable with, while the treatment was conducted according to a rigorous manual.

Also, in the assessment of treatment effects in the RCT, ratings of panic severity (i.e. panic-related distress and disability) and frequency of panic attacks were combined in one MANOVA. However, scores and changes on these measures are not necessarily highly related (Chambless, 1985; Craske & Barlow, 1988), and combining these measures in one analysis as was done here, could have diluted possible effects.

Sleep impairment was assessed using a self-report measure. Insomnia is a subjective disorder, and in the current study the assessment of subjectively rated sleep impairment within one sample was used to the advantage of investigating the current research questions. However, the role of cognitive inhibition should also be investigated using objective measures of sleep quality. Although sleep problems are known to be prevalent in patients with PD, it is

possible that these patients' anxiety lead to overestimations of experienced sleep problems. A recent study indicated that patients with PD differ on subjective and objective measures of sleep following psychopharmacological treatment (Todder & Baune, 2010). In that study, actigraphy was used as the objective measure of sleep, and even though the validity of this measure has been questioned (Sivertsen et al., 2006), the study by Todder and Baune (2010) underlines the need for further research to clarify this.

5.4 Ethical Considerations

There is always an ethical challenge when assigning participants to different treatment options in research. This is related to the core of this research, that one treatment is expected to be favourable over the other. In the study in the current thesis we expected the established treatment to yield better effects, but we wanted to assess the long-term and clinically significant effects of PE. This was important, as the recommended treatment for PD is currently scarcely available to those who need this treatment, while PE has been suggested as treatment for PD (Asmundson et al., in press; Otto et al., 2007; Smits et al., 2007). This did however mean that approximately half of the participants in the current study received the treatment that had a less certain clinical efficacy; PE.

The load related to assessments for those participating in treatment studies is also an important ethical consideration. PD is a disorder that is regularly assessed by a range of measures in treatment studies. The reason for this is that one is interested in detecting change both at a behavioural (i.e. mobility and avoidance) and cognitive level (i.e. fear of fear and sensitivity to bodily sensations). It is also important to know the frequency and severity of panic attacks. In addition, validity measures of general anxiety, depression and quality of life are generally recommended to determine whether changes relating to PD have had an impact

on other life domains. In the studies in the current thesis, we also wanted to investigate psychophysiology in these patients, and this obviously increased the load and time spent on assessments for the participants. This toll must always be weighed against the possible scientific value of the research questions. One obvious implication from this is that all data that are collected should be used to further scientific knowledge on PD and consequences of this disorder.

5.5 Conclusions and Recommendations

PE on its own appears to yield large and enduring reductions in anxiety and symptoms of panic disorder, albeit considerable smaller and less consistent than CBT. Importantly, PE did not lead to clinically significant change as assessed according to recommendations. Furthermore, we found measures of key executive functions to be related to vagally mediated HRV in patients with PD. This supports theoretical models linking cardiac regulation to activity in the prefrontal cortex, and demonstrates that this relationship is also present in anxious subjects, specifically in PD, the anxiety disorder most consistently linked do decreased vagally mediated HRV. Furthermore, results indicated that severity and duration of PD affects, or is affected by these same measures of cognitive and physiological flexibility. This is important, as PD is associated with increased mortality, supposedly mediated by the characteristically decreased HRV in these patients. Cognitive and possibly physiological flexibility were also found to be related to key measures of sleep impairment in patients with PD. This is in line with theoretical developments on insomnia. These findings first and foremost indicate the need for further research on the role of these measures as risk factors for clinical deterioration and development of co-morbidity in PD. PD and panic is associated with a more malign clinical course, and the findings that cognitive and physiological flexibility is

associated with sleep impairment and symptoms of insomnia is noteworthy. PD is the most frequent co-morbidity to depression (Roy-Byrne et al., 2000), a disorder that has also been associated with impaired cognitive inhibition, also following remission (Årdal & Hammar, 2011; Biringer et al., 2007; Hammar et al., 2010). Impaired executive functioning and reduced physiological flexibility has been suggested to constitute risk factors for development of anxiety and impairment associated with anxiety. If these factors are also related to the development of co-morbidity in PD, they should be considered targets for intervention, or be considered as outcome measures following treatment for PD. More should also be known regarding to what extent change on these psychophysiological variables is related to clinical change or lack thereof during treatment for anxiety.

PE can modulate measures of both these psychophysiological domains, and in the current thesis we have found PE to produce substantial and lasting effects on measures of PD and anxiety, although clinical changes following from PE appear not to be large enough to constitute clinical recovery. A natural suggestion following from these findings is that it should be assessed how the effects of PE can be harnessed and used in conjunction with an established treatment for anxiety such as CBT. This may provide an even more effective and robust treatment for PD, and especially if PE for PD also works through other mechanisms than only exposure to bodily sensations. However, from a societal perspective, combining CBT and PE as treatment for PD would not necessarily provide increased availability of treatment, as it often would require the presence of a therapist. Thus, the combination of PE and self-help or guided self-help would seem a more viable combination to provide additional available, effective and cost-effective treatment for PD. The feasibility and efficacy of such a combination could yield important insights, and possibly an improved intervention for patients suffering from this disorder.

6.0 References

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