Heart Rate Variability and Frontal EEG Asymmetry

as Markers of Psychological Pain

by

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DISSERTATION

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For the Master of the Universe, whose suffering world I do not comprehend

My Name is Asher Lev
Chaim Potok

He had denied his feminine side. Now, where is the wisdom in that?

This is the 21st Century
Marillion

But he wants so much not to live another lie. To be free and high again

The Sky Above The Rain
Marillion

Heading for the great escape, heading for the rave, heading for the permanent holiday, heading for the winter trip, heading for the slide, heading for the dignified walk away

The Great Escape
Marillion

Nothing ever goes away until it has taught us what we need to know

When Things Fall Apart
Pema Chödrön

Sterben werd' ich, um zu leben!

Symphony No. 2, Auferstehung
Gustav Mahler

So it's me I see, I can do anything. I'm still the child 'cos the only thing misplaced was direction. And I found direction. There is no childhood's end

Childhood's End?
Marillion

The greatest blessing that we have is the dawn of each new day

Happiness Is The Road
Marillion

Only love can stop you from merely existing

Sounds That Can't Be Made
Marillion

The wounds may have healed but the scars last forever

Exit Wound
Fish

It makes you suffer and it makes you cry, but it's all worthwhile

Hard As Love
Marillion

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Chapters 2 and 3 of this dissertation have been published in peer reviewed journals. Editorial changes have been made, in order to make them similar in appearance to other chapters of this dissertation. Chapter 2 is a reprint of the material as it appeared in the *Journal of Loss & Trauma (2011) 16(5)*, 402-412. The co-author listed in this publication directed and supervised the research that forms the basis for the dissertation.

Chapter 3 is a reprint of the material as it appeared in *Brain Imaging and Behavior (2013) 7(1)*, 1-14. The second author listed in this publication was a member of the dissertation committee, and provided feedback on the manuscript. The last author listed in this publication directed and supervised the research that forms the basis for the dissertation.

Abstract

Heart Rate Variability and Frontal EEG Asymmetry as
Markers of Psychological Pain
Esther L. Meerwijk

Introduction: Psychological pain is a frequently observed symptom in depression, and escape from unbearable psychological pain is often mentioned as the reason for suicide. We explored the relationship between psychological pain and two potential biomarkers: heart rate variability (HRV) and frontal EEG α-asymmetry. As both markers have successfully been used as feedback to alter mood state, knowledge about the relationship between HRV, frontal EEG, and psychological pain may be of particular interest for interventions to alleviate psychological pain.

Methods: Adults with a history of depression (N = 35) participated in six 5-minute sessions during which heart rate and EEG were recorded, while the participants sat upright with their eyes closed. In addition, participants completed the Beck scales for depression, hopelessness, and suicide ideation, and two measures of psychological pain: the Psychache Scale and the Orbach & Mikulincer Mental Pain (OMMP) Questionnaire.

Results: Mean age of the participants was 35.0 (*SD* 11.84) and their average level of depression and hopelessness was moderate. The intraclass correlation coefficient indicated excellent agreement of neurophysiological variables across successive measurements. In separate hierarchical regression models, after controlling for depression and hopelessness, low-frequency HRV and right midfrontal delta power contributed significant variance (ΔR^2 = 8.8%, β = -.30, p = .02 and ΔR^2 = 7.0%, β = -.26, p = .03, respectively) to the prediction of current psychological pain on the OMMP. For worst-ever psychological pain on the OMMP, midfrontal delta power contributed

significant variance (ΔR^2 = 20.5%, β = -.45, p = .004), after controlling for depression. Suicidal desire moderated the relationships of low-frequency HRV and midfrontal delta power to psychological pain on the Psychache Scale. High-frequency HRV and frontal α-asymmetry did not correlate with the Psychache Scale or OMMP scores. EEG asymmetry based on fractal dimensions decreased (greater left than right complexity) with increasing current and worst-ever psychological pain on the OMMP.

Conclusion: Findings suggest that greater psychological pain is associated with increased sympathetic nervous system activity, rather than with reduced parasympathetic nervous system activity. Psychological pain may affect the right frontal cortex more adversely than the left frontal cortex.

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General Introduction

Chapter 1

Pain is a symptom most human beings are familiar with. We learn empirically and at a young age that touching a hot stove and falling from your bicycle are unpleasant. Through these experiences, we learn to see pain as something that is primarily associated with physical injury (Merskey & Spear, 1967). *Psychological* pain does not necessarily involve physical injury and is conceptually different from physical pain. Psychological pain may accompany physical pain, but can exist without physical pain (Shneidman, 1999). Freud is recognized as the first to suggest that psychological factors could cause a pain-like experience (Fleming, 2008; Tyrer, 2006); a concept he called *Seelenschmertz,* which translates to 'pain of the soul', but is more commonly translated as mental pain. Indeed, many labels are used in the English literature to refer to the concept of psychological pain. Besides mental pain (Fleming, 2005; Orbach, 2003; E. Weiss, 1934), labels like emotional pain (Bolger, 1999; Tyrer, 2006) and psychic pain (Joffe & Sandler, 1967; Shattell, 2009) are used, whereas still others prefer to call it anguish (Maltsberger, 2004). Several authors have recently expressed a need for increased attention to the concept of psychological pain (Biro, 2010; Gaillard, et al., 2010; Shattell, 2009; Tossani, 2013).

Given the many ways to refer to what is essentially an unpleasant feeling, the research described in this dissertation started with a concept analysis of psychological pain. The results of that analysis are described in Chapter 2 and include a formal definition of psychological pain as "a lasting, unsustainable, and unpleasant feeling resulting from negative appraisal of an inability or deficiency of the self" (Meerwijk & Weiss, 2011). This definition was grounded in various theories and models of psychological pain, and intentionally structured similar to the definition of physical pain, to facilitate appreciation of the difference between the two concepts. Physical pain was defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Loeser & Treede, 2008, p. 475). Essential in the definition of psychological

pain is the cognitive aspect of negative appraisal; a characteristic that is not apparent in physical pain. Conversely, the definition of physical pain includes a reference to tissue damage; a characteristic that is absent in psychological pain. While a formal definition of psychological pain serves a clinical purpose and guides research, it is rather theoretical and devoid of the intense suffering that psychological pain sometimes represents. Therefore, it seems prudent to illustrate psychological pain with some examples.

Typical situations that may cause psychological pain are the loss of someone, especially a loved one, through death or divorce, loss of something that represents a core psychological need (e.g. a job, your health or autonomy, a safe place to live), or the inability to achieve something that represents a core psychological need (e.g. friendships, a university degree, or job position, but also the inability to prevent personal harm and shame). From a sociobiological perspective, psychological pain serves to draw attention to significant social events that have a negative effect on human desires and aspirations (Thornhill & Wilmsen Thornhill, 1989), to promote correction of events that caused the pain. Losses constitute a deficiency and may be acute, whereas an inability to achieve something essential is more likely to span a period of time. It is negative appraisal of these deficiencies and inabilities that causes psychological pain. Deficiencies and inabilities are especially relevant to chronic illnesses that severely impact one's life and anticipated future (e.g. major depression, posttraumatic stress, schizophrenia, multiple sclerosis). These illnesses may put a stop to the life one used to live, and may permanently prevent accomplishment of the goals one set out to achieve.

The remainder of this chapter contains a problem statement and describes the research aims, theoretical framework, and significance of the dissertation study that has been conducted. Beyond this general introduction, the organization of the dissertation is as follows. Chapter 2 describes a systematic analysis of the psychological pain concept. The definition of

psychological pain that is used throughout this dissertation is based on that concept analysis. Chapter 3 describes a review of brain imaging studies, and results in a tentative neural network involved in the experience of psychological pain. It is this review that prompted the study of frontal electroencephalography (EEG) asymmetry for this dissertation. Chapters 4 – 7 are based on data collected for this study. Chapter 4 will address associations between psychological pain and EEG frequency components, and whether frontal EEG asymmetry predicts psychological pain. Chapter 5 will focus on the relationship between psychological pain and heart rate variability. The effect that completing questionnaires on psychological pain has on frontal EEG asymmetry and heart rate variability will be addressed in Chapter 6. Chapter 7 will focus on the questions of whether heart rate variability predicts psychological pain and whether the relationships of frontal EEG asymmetry and heart rate variability to psychological pain are moderated by suicidal desire. A final general discussion (Chapter 8) will synthesize and interpret the findings of this study, and identify implications for future research.

Problem Statement

Research has shown that we know little about the prevalence of psychological pain (Mee, Bunney, Reist, Potkin, & Bunney, 2006). A recent study (Olié, Guillaume, Jaussent, Courtet, & Jollant, 2010) assessed psychological pain in patients hospitalized for a major depressive episode and found that 51.4% experienced high current psychological pain (score > 7 on a numerical rating scale ranging from 0 to 10). Pompili, Lester, Leenaars, Tatarelli, and Girardi (2008) used a similar scale (range 1 – 9) to assess psychological pain in psychiatric inpatients. They found a mean current psychological pain level of 6.66 (Standard Deviation [*SD*] 2.10) and a mean worst-ever psychological pain of 8.59 (*SD* 0.67). Another recent study in patients admitted for a depressive episode (van Heeringen, Van den Abbeele,

Vervaet, Soenen, & Audenaert, 2010) reported a mean current psychological pain score of 135 (*SD* 32.2, theoretical range 44 – 220) on the Orbach & Mikulincer Mental Pain questionnaire. Using the same questionnaire, Reisch et al. (2010) assessed psychological pain in patients who had recently attempted suicide. Their results corresponded to a mean psychological pain score of 148.3. These studies unequivocally show high levels of psychological pain in people with mental illness, especially in patients diagnosed with a depressive disorder.

Research suggests that depressive symptoms, hopelessness, and suicidality, may be highly correlated with psychological pain. Evidence for these covariates stems from nonclinical samples involving students (DeLisle & Holden, 2009; Holden, Mehta, Cunningham, & McLeod, 2001; Leenaars & Lester, 2004; Lester, 2000; Orbach, Mikulincer, Sirota, & Gilboa-Schechtman, 2003b; Troister & Holden, 2010), prison inmates (Mills, Green, & Reddon, 2005), and the general population (Soumani, et al., 2011). Some studies also reported significant correlations with psychological pain in psychiatric samples. A study of psychiatric inpatients (Pompili, et al., 2008) found a small positive correlation between worst-ever psychological pain and hopelessness ($r = .28$, $p = .009$, $N = 88$). Another study (Orbach, Mikulincer, Gilboa-Schechtman, & Sirota, 2003a) compared psychiatric inpatients who had attempted suicide ($n = 32$) with patients without such history ($n = 29$) and healthy adults from the general population ($n = 30$). It was found that various aspects of psychological pain correlated positively with depression and hopelessness, with correlation strengths ranging from .27 to .59 ($p < .01$). Van Heeringen et al. (2010) reported a moderate positive correlation between psychological pain and suicide ideation ($r = .43$, $p < .05$, $N = 39$) and a strong positive correlation with hopelessness ($r = .52$, $p < .001$).

Research into psychological pain is gradually expanding, but we still know very little about the exact role of psychological pain in mental

well-being or about markers that are associated with psychological pain. A systematic review of brain function studies (see Chapter 3) found an asymmetry in frontal brain activity while study participants experienced or recalled psychological pain. Predominant decreased activity was found in the right ventromedial prefrontal cortex, whereas the left ventromedial prefrontal cortex slightly favored increased activity. Several investigators have suggested a connection between right medial frontal brain activity and the autonomic nervous system (Hilz, et al., 2006; Tanida, Sakatani, Takano, & Tagai, 2004; Thayer, 2009). Heart rate variability, the oscillation in interval between consecutive heartbeats, is a marker of autonomic nervous system function (American Heart Association, 1996).

Both asymmetry in frontal brain activity, particularly resting-state frontal EEG asymmetry, and heart rate variability are well studied in relation to depression (Kemp, et al., 2010b; Thibodeau, Jorgensen, & Kim, 2006). Thibodeau et al. (2006) did an extensive meta-analysis of studies on resting-state frontal EEG asymmetry in the alpha frequency band (8 – 13 Hz), in people who experienced depression. Despite existing publication bias toward studies reporting significant findings, their analysis convincingly showed greater right than left frontal alpha activity in depressed individuals. Later studies in people who were diagnosed with major depressive disorder (Kemp, et al., 2010a) and in healthy people with depressive symptoms (Mathersul, Williams, Hopkinson, & Kemp, 2008) confirmed the findings of Thibodeau et al.. Greater right than left frontal alpha activity seems at odds with the review presented in Chapter 3, which found a predominant decrease in right-sided activity. However, the result of that review likely reflects an outcome across the entire frequency range, whereas Thibodeau's et al. (2006) meta-analysis specifically focused on activity in the alpha frequency range. This suggests that the decrease in right-sided activity is due to activity changes in frequency bands other than alpha.

In another meta-analysis, Kemp et al. (2010b) evaluated the impact of depression on resting-state heart rate variability. Their analysis indicated lower high-frequency heart rate variability in unmedicated patients with major depressive disorder compared to healthy people, but no differences were found in low-frequency heart rate variability. Low-frequency heart rate variability and high-frequency heart rate variability apply to variability in the 0.04 – 0.15 Hz and 0.15 – 0.4 Hz frequency range, respectively (Malik, 1996). Recent studies reported lower heart rate variability in unmedicated patients (H.-A. Chang, et al., 2012b; J. S. Chang, et al., 2012; Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012) and corroborated the meta-analysis, however, null results were also reported (Licht, Penninx, & de Geus, 2011; Schulz, Koschke, Bär, & Voss, 2010). The meta-analysis also reported differences in heart rate variability based on nonlinear measures, that is measures based on nonlinear dynamical systems theory (Shelhamer, 2007).

Heart rate variability and frontal EEG asymmetry have been studied extensively with respect to depression, but neither were studied within the context of psychological pain. Therefore, the purpose of this dissertation study was to explore the relationships between resting-state heart rate variability, frontal EEG α-asymmetry, and psychological pain in adults with a history of depression. Combining the physiological perspective (heart rate variability) and neuropsychological perspective (frontal EEG asymmetry) into one study enriches inferences about the phenomenon of psychological pain (Cacioppo, 2004). Previous research has shown that people with a history of depression were likely to experience psychological pain, and would provide an adequate range of psychological pain intensity in the study sample.

CHAPTER 1

Research Aims

This dissertation study had the following primary aims:

1. To determine whether resting-state frontal EEG α-asymmetry predicts psychological pain, after controlling for depression, hopelessness, and suicide ideation.
2. To determine the direction of associations between psychological pain and resting-state frontal activity in standard EEG frequency bands, while controlling for selected covariates.
3. To determine whether heart rate variability predicts psychological pain, after controlling for depression, hopelessness, and suicide ideation.
4. To determine whether resting-state frontal EEG α-asymmetry and heart rate variability are decreased after completion of questionnaires on psychological pain, when compared to a baseline recording.

In addition, a secondary aim of the study was to compare traditional analytic approaches of frontal EEG α-asymmetry and heart rate variability with a measure based on nonlinear dynamical systems theory (Shelhamer, 2007). Hereafter, the prefix α before asymmetry will often be omitted, but α-asymmetry is implied.

Theoretical Framework

Heart rate variability and frontal EEG asymmetry are linked through the autonomic nervous system, which comprises the sympathetic and the parasympathetic nervous systems (Sherwood, 2010). These components of the autonomic nervous system have opposing effects. With respect to

cardiovascular function, activation of the sympathetic system increases heart rate, whereas activation of the parasympathetic system inhibits heart rate. Both systems exert their influence simultaneously; however, the sympathetic nervous system is dominant in states of arousal, which is commonly referred to as the 'fight or flight' response. The parasympathetic nervous system on the other hand, is dominant when the body is at rest, which is commonly referred to as 'rest and digest' (Sherwood, 2010). One of the defining characteristics of psychological pain is that it is a lasting feeling (see Chapter 2), which may exert its neurophysiological effects whether the body is at rest or not. In Chapter 3, it is suggested that psychological pain is associated with increased emotional arousal. Arousal typically involves increased heart rate (Critchley, Corfield, Chandler, Mathias, & Dolan, 2000; Sherwood, 2010; Tanida, et al., 2004) and reduced heart rate variability (Porges, 2007; Siepmann, Aykac, Unterdorfer, Petrowski, & Mueck-Weymann, 2008). Studies of cardiovascular function and the prefrontal cortex suggested that the right ventromedial prefrontal cortex may have a prominent effect on heart rate in response to emotionally arousing stimuli (Hilz, et al., 2006; Tanida, et al., 2004), and that a neural network that includes the right medial prefrontal cortex plays a role in parasympathetic control over heart rate (Thayer, 2009). These considerations, together with research that was discussed as part of the problem statement, lead to the following hypotheses:

1. Greater psychological pain will be associated with relative right (greater right than left) frontal alpha activity.
2. Greater psychological pain will be associated with less right frontal activity in frequency ranges other than alpha.
3. Greater psychological pain will be associated with less heart rate variability.
4. The postulated state of arousal evoked by psychological pain results from decreased parasympathetic activity.

CHAPTER 1

Circumplex Model of Affect

Psychological pain is unpleasant by definition, and it was suggested that psychological pain is associated with increased arousal. These two facets are elegantly combined in the circumplex model of affect (Russell, 1980), which holds that human affect is the result of a cognitive process that is organized along two orthogonal dimensions: pleasure and arousal. The pleasure dimension, ranging from unpleasant to pleasant, is more commonly called valence (Harmon-Jones, 2004; Posner, Russell, & Peterson, 2005). The arousal dimension in the proposed model ranged from sleepy to aroused (Russell, 1980), but is also depicted as ranging from low arousal to high arousal (Posner, et al., 2005). The model is based on psychological research in which participants classified and ordered affect labels. Figure 1.1 is a reproduction (Russell, 1980) that shows typical results of that process. The resulting model contains affect labels roughly in a circular shape, with the two dimensions crossing at the circle origin. The coordinates along the vertical and horizontal axes represent varying degrees of valence and arousal. The model is generally supported (Fontanari, Bonniot-Cabanac, Cabanac, & Perlovsky, 2012; Kring, Barrett, & Gard, 2003), but mixed results were also found (Remmington, Fabrigar, & Visser, 2000).

Posner et al. (2005) have reviewed neurophysiological research that supports the valence and arousal aspects of affect independently of each other. They proposed that the two dimensions of the circumplex model are each supported by a neural network, the complex interaction of which determines the resulting affective experience. They hypothesized that the valence dimension is supported by the mesolimbic pathway, which is a dopaminergic pathway in the brain. This pathway is thought to be involved in pleasure, reward, and motivation (Nestler & Carlezon, 2006; Salamone & Correa, 2012). Posner et al. furthermore hypothesized that the arousal network involves the reticular formation, which regulates the sleep-wake

cycle (Brown, Basheer, McKenna, Strecker, & McCarley, 2012; Reinoso-Suarez, de Andres, & Garzon, 2011). Both the arousal network and the mesolimbic pathway include the prefrontal cortex, which is thought to link valence and arousal experiences to past experiences and future consequences. Support for independent neural networks that underlie valence and arousal has been reported (Colibazzi, et al., 2010; Gerber, et al., 2008; Nielen, et al., 2009; Posner, et al., 2009).

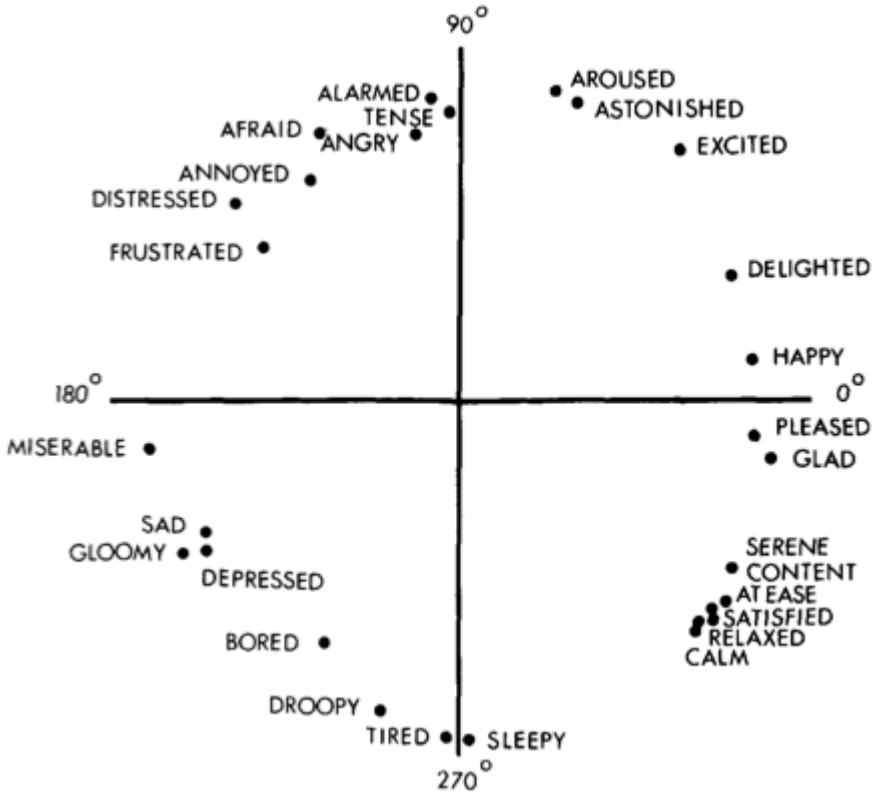

Figure 1.1 Typical result of affect label ordering, showing the valence (horizontal) and arousal (vertical) dimensions of the circumplex model of affect (reproduced from Russell, 1980).

Two variables that are relevant to the circumplex model of affect and that will be addressed in this study, are frontal α-asymmetry and heart rate variability. As discussed earlier, greater right than left frontal alpha activity was linked to feelings of depression, which makes frontal α-asymmetry an index of the pleasure dimension of the circumplex model. Heart rate variability was associated with emotional arousal and is an index of the arousal dimension of the model.

Significance

Study of psychological pain is important for several reasons. First and foremost, knowing which neurophysiological mechanisms underlie the experience of psychological pain provides a basis for the development of therapy that may alleviate psychological pain. Alleviation of pain and suffering is a fundamental nursing responsibility (American Nurses Association, 2005; International Council of Nurses, 2001). Moreover, psychological pain does not only adversely affect mental health. Growing evidence points to the negative effects of poor mental health on physical well-being (Prince, et al., 2007; S. J. Weiss, Haber, Horowitz, Stuart, & Wolfe, 2009), and the World Health Organization (WHO) contends that there is no health without mental health (WHO, 2007). Alleviation of psychological pain could lead to decreased disability and improved quality of life (Shattell, 2009). One of the ways neurophysiological markers may facilitate alleviation of psychological pain is through the application of biofeedback. Both heart rate variability and frontal EEG asymmetry have successfully been used to change mood state through interventions based on biofeedback (Hassett, et al., 2007; Reiner, 2008; Siepmann, et al., 2008) and neurofeedback (Allen, Harmon-Jones, & Cavender, 2001; Baehr, Rosenfeld, & Baehr, 2001; Choi, et al., 2011).

Second, up till now only self-report measures (Holden, et al., 2001; Orbach, et al., 2003b) of psychological pain are available. Self-report instruments are inherently subjective, which can be an advantage if little is known about the phenomenon that is measured. However, subjectivity brings with it the risk of response bias (Polit & Beck, 2004, p. 359). Respondents may have a tendency to select extreme answers, either positive or negative, when offered a set of response options. Other respondents may prefer the opposite and "keep to the middle of the road". Another phenomenon is caused by social desirability, i.e. people tend to present a more favorable picture of themselves. The ability to assess psychological pain through its neurophysiological markers provides a measure unbiased by personal objectives or interpretations. Such an objective measure can be useful to assess therapy efficacy (e.g. drugs, biofeedback). An objective measure may also be able to identify people who are more likely than others to respond to therapy and can be used to determine optimal treatment dosages.

Third, neurophysiological markers of psychological pain may have diagnostic value in clinical situations, most specifically when a patient requests euthanasia. Under strict criteria of due care, euthanasia is allowed in some European countries (Luxembourg, Belgium, Netherlands), and forms of physician-assisted dying are legal in Switzerland and the U.S. states of Oregon and Washington (Buiting, et al., 2009). One of the criteria for euthanasia is an assessment of whether the patient perceives his or her suffering as unbearable. Sources of suffering may be physical and psychological in nature, and it is notably easier to establish intolerable suffering in a patient whose suffering has physical causes (Buiting, et al., 2008). Suffering and psychological pain refer to the same experiential phenomenon (Meerwijk & Weiss, 2011), where suffering refers to the behavioral aspects of experiencing psychological pain. The ability to assess intractable suffering through neurophysiological markers of psychological pain

could provide additional information for clinical decision making regarding euthanasia.

A final argument in support of studying neurophysiological markers of psychological pain involves clinical patients with manifest psychological pain who may be suicidal. Significant associations were found between psychological pain and suicide ideation (Holden, et al., 2001; Leenaars & Lester, 2004; Lester, 2000; Troister & Holden, 2010, 2013; van Heeringen, et al., 2010) and between psychological pain and a history of suicide attempt (Holden, et al., 2001; Orbach, et al., 2003a). In the only prospective study to date (Troister & Holden, 2012), psychological pain in high-risk students was found to covary with suicide ideation over time. The risk for suicide in people with severe mental illness (e.g. schizophrenia, depression, bipolar disorder) is especially high immediately after hospital discharge (American Psychiatric Association, 2003; Troister, Links, & Cutcliffe, 2008). An objective assessment of psychological pain before hospital discharge may identify patients who are more likely to attempt suicide after discharge. Thus, an assessment of psychological pain that does not rely on self-report may help reduce suicide risk, in that appropriate measures may be taken (e.g. extended hospital stay or stay with a significant other).

Two

Toward a Unifying Definition of Psychological Pain

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CHAPTER 2

Psychological pain is prominent in loss and trauma but its prevalence has not been systematically studied (Mee, et al., 2006). However, psychological pain has been identified as the most frequently mentioned reason for suicide (Chavez-Hernandez, Leenaars, Chavez-de Sanchez, & Leenaars, 2009; R. C. O'Connor, Sheehy, & O'Connor, 1999). Using data on suicide ideation as a proxy for the prevalence of psychological pain, millions of people may experience psychological pain in the U.S. alone, including 5.6% in the general U.S. population and 53% in patients with severe mental illness (American Psychiatric Association, 2003). Such estimates are clearly conservative since suicide is an extreme outcome of psychological pain.

Alleviation of psychological pain, like alleviation of physical pain, is a fundamental responsibility of health professionals. In 2009, Shattell questioned why the criteria for pain management put forward by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) do not include psychological pain or psychic pain as she called it. In her call for psychological pain awareness, Shattell used various labels of suffering, emotional pain, mental or emotional distress, and psychic or emotional suffering to refer to psychological pain. Possibly the closest proper definition was offered by Orbach and colleagues who defined mental pain as "a wide range of subjective experiences characterized as an awareness of negative changes in the self and in its functions accompanied by negative feelings" (Orbach, et al., 2003b, p. 228). This definition describes a very general state of negative change and negative feelings. More recently, psychological pain was defined by merely distinguishing it from physical pain: "a diffuse subjective experience ... differentiated from physical pain which is often localized and associated with noxious physical stimuli" (Mee, et al., 2006, p. 681).

While these definitions provide an initial foundation for understanding psychological pain, the use of various labels or very general definitions to refer to the same or a similar experience is an indication that a

concept is not mature (Morse, Mitcham, Hupcey, & Tason, 1996). In light of the many people who may suffer from psychological pain, a clearer conceptualization seems warranted as a basis for future research and treatment. The purpose of this paper is to develop a definition of psychological pain that describes its specific features through a concept analysis and synthesis of existing literature. Descriptions of psychological pain offered by different theories and models will be evaluated and serve as the basis for a more precise and unifying definition of psychological pain.

Theories and Models Associated with Psychological Pain

Literature for this concept analysis was searched in computerized databases (Medline, PsycINFO, CINAHL), with no restriction on year of publication. Publications were included if they matched the combination of search terms for psychological pain and the terms theory, model, or concept. Search terms for psychological pain included psychological pain, mental pain, psychic pain, psychache, emotional pain, suffering, anguish, and torment. Standardized keywords (MESH, thesaurus terms, CINAHL headings) were used if available. Combinations of these terms resulted in 691 hits, while limiting to articles published in English. After assessing the titles for applicability, 57 articles remained of which the abstracts were read. Based on these abstracts, another 51 articles were excluded because they did not present a theory or model of psychological pain. The remaining six articles were obtained, and five more articles were traced via reference lists. Among these articles, five perspectives on psychological pain were identified that described a theory or model in sufficient detail to allow for concept analysis in this paper's discussion. These perspectives were (a) discrepancy in self-representation (Joffe & Sandler, 1967), (b) psychache (Shneidman, 1993), (c) emotional pain (Bolger, 1999), and (d) two models of suffering (Morse, 2001; Rehnsfeldt & Eriksson, 2004). Each of these perspectives is briefly introduced in the following section, with more detailed analysis in the discussion.

According to Joffe and Sandler (1967), psychological pain results from a discrepancy between the ideal and actual perceptions of the self. This self-schema, or self-representation (Sandler, 1962), consists of mental images that a person has of his/her psychological and social being, and was an extension of the body schema described by Head in 1926. As an example, a person may have an ideal schema of being highly successful and admired, but an actual schema that reflects failure and being ignored. Psychological pain is the affective state associated with this discrepancy and varies over time, as the ideal or actual self-schemas vary depending on internal and external circumstances (Sandler, 1962). From Joffe and Sandler's (1967) point of view, pain should be broadly defined and encompass both physical and psychological pain, or in their terminology, bodily pain and psychic pain. They saw the basic quality of all pain as an unpleasant feeling associated with a wide array of ideational content. The severity of this feeling could range from slight discomfort to acute physical distress. They also referred to the experience of pain as suffering.

In 1993, Shneidman introduced the notion of psychological pain as psychache, a term he used to refer to intolerable psychological pain. In his words, psychache is "the hurt, anguish, soreness, aching, psychological *pain* [*sic*] in the psyche, the mind" (Shneidman, 1993, p. 145). In later work, he defined psychological pain as an introspective experience of negative emotions (1999). Shneidman proposed that extreme psychache is inextricably connected to suicide and indicates that the hurt is too much to bear. The origin of psychological pain, according to Shneidman, is best explained by frustrated psychological needs as originally described by Murray (1938/2008). Based on more than 40 years of clinical experience, Shneidman (1998) found that psychache leading to suicide often involved frustration of the needs to (a) affiliate; (b) be supported, protected and loved; (c) avoid humiliation and embarrassment; (d) make up for a loss; (e) vindicate oneself of blame or criticism; (f) protect oneself and one's psychological space; (g) achieve a sense

of organization in one's life; or (h) find answers to important unresolved issues or questions.

The third perspective on psychological pain is Bolger's model of emotional pain (1999). She defined emotional pain as a feeling of brokenness resulting from a traumatic event, which suddenly shatters the external cover that represents a person's identity and facilitates connection with others. Three states of the self are represented in Bolger's model: (a) covered, (b) broken, and (c) transformed. Emotional pain is the central aspect of the broken self, which is characterized by woundedness or injury, loss of self or wholeness, disconnection within self and from others, and a critical awareness of one's negative attributes (Bolger, 1999). This latter awareness, including one's role in creating potential problems, is viewed as a critical component in understanding and making sense of emotional pain. Bolger described how experiencing the pain has a strengthening effect over time because a person realizes that the pain can be survived. This creates confidence and a new understanding about the self, which leads to the transformed self.

In Morse's model of suffering (2001) suffering is considered a necessary means to recovery. She based her model on extensive research with patients from trauma and burn units, patients with chronic conditions, and patients from oncology and palliative care populations. The model has two behavioral states, labeled 'Enduring', which involves emotional suppression, and 'Emotional suffering', which involves emotional releasing. Suffering can arise from various social, psychological, emotional, and physical situations. However, in her description of the model, Morse (2001) mainly referred to suffering in response to a loss. In the enduring state, a person blocks emotional responses, which enables the person to keep going and function as the situation requires. In contrast, the state of emotional suffering involves expression of emotions and recognition of what caused the suffering and the changed future that lies ahead. According to Morse (2001), when one has suffered enough, hope for an alternative future will grow, and when hope

has grown enough, one may come to acceptance. If a person is not ready to accept yet, feelings of psychological disintegration may move a person back into the state of enduring.

The final perspective on psychological pain is the model of suffering by Rehnsfeldt and Eriksson (2004). Eriksson (1992) saw suffering in terms of human existence and initially defined suffering as not being able to hold oneself together as a whole. The process of suffering was seen as a movement from unbearable to bearable suffering. Rehnsfeldt and Eriksson (2004) later described unbearable suffering as a darkness in the understanding of life during which no existential meaning can be found in an event that caused the suffering and its consequences. In order to reach a state of bearable suffering, a person has to cross a turning point that involves a decision to continue living over dying. This marks the moment the struggle of suffering begins - a struggle that is characterized by a constant shift between hope and hopelessness, meaning and meaninglessness, reconciliation and broken-heartedness (Rehnsfeldt & Eriksson, 2004). Bearable suffering, in their view, is a continuous force that drives the person to find meaning.

Discussion

In the following discussion, we critically examine differences and commonalities in how the concept of psychological pain is described when viewed through the varied perspectives of psychache, suffering, emotional pain, and discrepancy in self-schema. Criteria proposed by Morse, Mitcham, Hupcey, and Tason (1996) are used to inform our concept analysis because of their utility in evaluating specific features of concepts. Morse et al. have identified five structural features that together make up the anatomy of a concept: (a) definition, (b) characteristics, (c) boundaries, (d) preconditions, and (e) outcomes. These five features are applied to the various perspectives as the basis for a unifying definition of psychological pain.

Definitions of Psychological Pain

Definitions are meaningful descriptions that enable identification of and reference to the concept they describe (Morse, et al., 1996). Joffe and Sandler's (1967) discussion of psychological pain as a discrepancy in self-schema did not explicitly define psychological pain. However, they did note that the basic quality of psychological pain is a state involving unpleasant feelings. Shneidman (1999) defined psychological pain as an experience of negative emotions and also referred to it as hurt, anguish, soreness, aching in the psyche or mind. Bolger (1999) defined emotional pain as a state of feeling broken that involved the experience of being wounded, loss of self, disconnection, and a critical awareness of one's more negative attributes. Morse (2001) did not define psychological pain per se but her description of suffering refers to an affective state of discomfort, anguish, distress, torment, pain, heartache, and misery. Eriksson and Rehnsfeldt (2004) defined suffering as not being able to hold oneself together as a whole.

Common across all these definitions is the experience of unpleasant feelings such as negative emotions or misery. In addition, the definitions for emotional pain (Bolger, 1999) and for suffering according to Rehnsfeldt and Eriksson (2004) both refer to a sense of personal disintegration. Morse (2001) referred to this experience as psychological disintegration. However, the definitions are quite abstract, reducing their value as a means to identify the concept they describe. Moreover, neither Shneidman nor Joffe and Sandler identified disintegration as a component of psychological pain.

Characteristics

Characteristics are attributes that must be present in all instances of a concept, although they may vary in strength or form (Morse, et al., 1996). A primary characteristic of psychological pain appears to be the

individual's negative appraisal of a deficient self. For instance, Joffe and Sandler (1967) note that psychological pain results from a cognitive discrepancy between the ideal and actual self, suggesting negative appraisal of a self that is lacking some desired quality. Shneidman (1999) mentioned psychological pain being an introspective experience in response to frustrated needs, which also suggests negative appraisal of a deficient self. Central characteristics of emotional pain are described as a sense of loss or incompleteness of self and an awareness of one's own role in the experience of emotional pain (Bolger, 1999). These features also indicate a conscious awareness and point to negative appraisal of feeling incomplete. Morse (2001) clearly identified a person's recognition of what caused the suffering as a characteristic of suffering, along with negative appraisal of resulting consequences for the self. Bearable suffering, described by Rehnsfeldt & Eriksson (2004) as a search for meaning, also suggests negative appraisal of a personal state without meaning. Unbearable suffering reflects an even greater perceived deficiency, including meaninglessness and hopelessness.

A second characteristic common to all five perspectives is that psychological pain takes time to resolve. While its onset may be either acute or develop over time, the impact of psychological pain is not short lived but appears to endure. A third and related characteristic is the untenability of psychological pain, which has to be resolved to avoid serious negative consequences. Morse (2001) addressed this characteristic in regard to 'enduring suffering', whereby the experience cannot continue indefinitely but rather needs to be resolved. The characteristic can also be found in Shneidman's account of psychache (1993) when he speaks of intolerable and unbearable psychological pain, and in what Rehnsfeldt and Eriksson (2004) describe as a decision to live or die. Bolger (1999) mentioned that pain can be destructive and leave someone irreparably damaged, and Joffe & Sandler (1967) suggested potential pathogenic consequences of enduring psychological pain.

This analysis indicates that three characteristics of psychological pain are common across all perspectives, although they are mentioned more explicitly in some perspectives than others. In sum, psychological pain involves negative appraisal of a deficient self, is a lasting experience, and cannot be sustained indefinitely without adverse consequences.

Boundaries

Morse et al. (1996) described boundaries of a concept as parameters that indicate "when an exemplar is no longer an instance of a particular concept" (p. 386). There are three situations in which concept boundaries are crossed: (a) not all attributes are present, (b) attributes are weak, and/or (c) new attributes appear that are not considered characteristic of the concept of interest. Our analysis of boundaries compares psychological pain to physical pain, depression, and hopelessness – concepts whose attributes are often linked to psychological pain.

Physical pain has been defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Loeser & Treede, 2008, p. 475). Tissue damage was not mentioned in any description of psychological pain. While emotional experiences are discussed in descriptions of psychological pain, these experiences are not related to tissue damage but rather to mental experience. In addition, physical pain is not necessarily a lasting experience and does not involve the awareness of a deficient self, both of which are identified characteristics of psychological pain.

Depression does not necessarily involve an experience of personal disintegration or being deficient in areas of the self. Although major depression as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2000) may involve these characteristics, it exceeds them by also involving criteria such as anhedonia,

significant weight changes, insomnia or hypersomnia, and fatigue or loss of energy. However, psychological pain, as a symptom, may well be present in major depression and a wide range of other mental and physical disorders or diseases (e.g. AIDS, fibromyalgia, multiple sclerosis, schizophrenia, borderline personality disorder, post-traumatic stress disorder).

Hopelessness is a feeling that one's physical, emotional, or social state is beyond improvement. As noted earlier, one may be hopeless when experiencing psychological pain (Rehnsfeldt & Eriksson, 2004). However, characteristics like an incomplete or disintegrating self and the untenable nature of the experience are not intrinsic to hopelessness. In addition, hopelessness that has its origin in external conditions may be more easily resolved than psychological pain in situations where these conditions are improved.

This comparison to identify boundaries of psychological pain shows that not all characteristics of psychological pain are present in physical pain, depression and hopelessness, or that new characteristics appear that were not identified as belonging to psychological pain.

Preconditions

Morse et al. (1996) suggested that *all instances* of a concept must be preceded by similar conditions. Joffe and Sandler (1967) mentioned failure to achieve an ambition, loss of a love-object, and extreme guilt or shame as possible conditions that could lead to a discrepancy between the ideal and actual self - their proposed cause of psychological pain. Similarly, Shneidman (1993) referred to a difference between a desirable state and reality as the cause of psychological pain, which he called frustrated psychological needs. Examples Shneidman used were excessively felt shame, guilt, humiliation, loneliness, fear, angst, and dread of growing old or of dying badly. Both Joffe and Sandler and Shneidman appear to view loss of something/someone

desirable (a loved one, health) or failure to achieve something desirable or avoid something undesirable as possible preconditions of psychological pain.

Morse (2001) also mentioned loss as a major cause of suffering. Examples she gave were loss of a pain-free existence, loss of dignity, loss of movement, loss of an anticipated future, loss of another, and loss of self. Although Morse primarily focused on loss of something/someone desirable as a precondition for psychological pain, the loss of an anticipated future, as described in her theory, could be considered a failure to achieve something desirable.

Bolger (1999) described emotional pain as something that is triggered by a traumatic event. Examples of such events she gave were deaths, abuse, neglect, divorce, illness and illness of significant others. Death, especially of a loved one, and illness can be viewed in terms of a loss, as discussed before. When viewed in terms of frustrated psychological needs as did Shneidman, abuse can be seen as a frustration of the need to protect the self and one's psychological space. Neglect and divorce may be seen as a frustration of the need for affiliation with another. Traumatic events can also be viewed as a loss of psychological security or the ability to defend oneself.

Preconditions for suffering as described by Rehnsfeldt and Eriksson (2004) are unclear. They speak of a darkness in the understanding of life and an absence of existential meaning. What causes this darkness and absence of meaning remains somewhat vague. However, when viewed as a frustrated psychological need (Shneidman, 1998), lack of understanding can be seen as a precondition for psychological pain. In addition, failure to achieve understanding is one example of the failure to achieve something desirable.

Overall, it appears that the preconditions for psychological pain can be described in terms of either the loss of something/someone desirable or a failure to achieve something desirable (or the converse - to avoid something undesirable). Frustrated psychological needs as suggested by Shneidman can be seen as a more detailed representation of these two conditions.

CHAPTER 2

Outcomes

All cases of a concept, such as psychological pain, should have similar outcomes whenever they occur, presumably across the broad range within which a concept may occur (Morse et al., 1996). Although the focus of Joffe and Sandler's (1967) description of psychological pain was primarily on definition and attributes, they did discuss adaptation to pain and its advantages for development as an outcome. They noted that the response to pain could also be pathogenic, with development of severe depression as one potential outcome (Joffe & Sandler, 1967).

Suicide is probably the most radical outcome of psychological pain. Psychological pain does not necessarily result in suicide, as people have different thresholds for the level of psychological pain they can endure (Shneidman, 1993). An individual's unique tolerance for psychological pain may influence how much a person can bear before becoming overwhelmed. It is reasonable to assume that the frequency, duration and intensity with which extreme negative emotions are experienced will also affect the likelihood of exceeding that threshold.

The models and theories for emotional pain (Bolger, 1999) and suffering (Morse, 2001; Rehnsfeldt & Eriksson, 2004) are in sharp contrast with Shneidman's view on psychological pain, as emotional pain and suffering are described as potentially healing experiences. Although she did mention that emotional pain can have a destructive effect, Bolger (1999) predominantly described the strengthening effect of emotional pain, which leads the broken self to the transformed self. Morse (2001) mentioned how hope for an alternative future will grow when one has suffered enough, which leads to a reformulated self. According to the model of suffering by Rehnsfeldt and Eriksson (2004), the desired outcome of suffering is to find meaning. If meaning is not attained, the person will remain in a state of unbearable suffering. None of the theories for suffering described what

happens when healing does not occur after a prolonged period of time, although Rehnsfeldt and Eriksson (2004) mentioned that a patient stops growing when unbearable suffering persists.

Across all perspectives, the outcomes of psychological pain are predominantly described as having the potential for personal growth. This conceptualization of psychological pain is congruent with Frankl's view of suffering. He noted: "When we are no longer able to change a situation ... we are challenged to change ourselves, " and "suffering ceases to be suffering at the moment it finds a meaning" (Frankl, 1984, pp. 116-117). However, the various perspectives on psychological pain also recognize that serious adverse outcomes such as psychopathology and suicide may occur.

Conclusions

The fact that different labels and definitions are being used to refer to experiences with similar characteristics and outcomes provides evidence that psychological pain as a concept is still in its infancy (Morse, et al., 1996). However, our analysis of various theories and models indicates that suffering, emotional pain, psychache, and psychological pain essentially refer to the same experience.

Consistent use of the term 'psychological pain' in clinical practice and research may be advantageous for two reasons. First, across all theories and models that were examined, references to pain metaphors were recurrent (hurt, soreness, aching, woundedness, being injured, being ripped apart, torment, heartache, broken-hearted). People often experience psychological pain as a pain in the stomach, heart or head. Labeling a concept in the way people actually describe it (e.g. pain rather than suffering) allows for clearer communication about that concept. Second, the term psychological pain seems more appropriate than emotional pain because theorists also describe cognitive components of the concept, especially in the appraisal of a deficient

self. In contrast to the term emotional, the term 'psychological' encompasses beliefs, thoughts, feelings, and behaviors (Covington, 2000). Psychological pain is also preferable to mental or psychic pain because the adjective psychological may allow for broader acceptability and understanding among patients and diverse professional disciplines.

Table 2.1 Core descriptors of psychological pain.

Characteristics

- An unpleasant feeling, often experienced as a disintegration of the self
- Negative appraisal of an inability or deficiency of the self
- A lasting state of being that takes time for resolution
- A state of being that is impossible to sustain over time without serious negative consequences

Preconditions

- Loss of someone/something associated with an important psychological need
- Failure to achieve something associated with an important psychological need

Outcomes

- Positive
    - Adaptation and personal growth
    - Enhanced sense of meaning
- Negative
    - Pathology (mental and potentially physical)
    - Suicide

Based on our concept evaluation, psychological pain is being defined as a lasting, unsustainable, and unpleasant feeling resulting from negative appraisal of an inability or deficiency of the self. Table 2.1 outlines our synthesis of the characteristics, preconditions, and outcomes that describe psychological pain. It involves a cognitive appraisal that the self is deficient or lacking in some degree of wholeness. This appraisal is typically brought on by loss of or failure to achieve an important object or outcome that is intimately linked to core psychological needs. The resulting psychological pain is neither easily resolved nor is it possible to sustain over time without serious consequences. When unresolved, pathology or even suicide may be the outcome. If resolved effectively, psychological pain may be a healing experience, enhancing psychological adaptation, personal growth, and greater meaning in life.

Psychological pain has inherent significance for the field of loss and trauma. Individuals with whom we work endure a myriad of stressful experiences that reflect the very preconditions for psychological pain. It is our hope that the clarification of the psychological pain concept, provided in this paper, can facilitate further research to explicate the characteristics and preconditions associated with psychological pain and how they may influence therapeutic versus pathogenic outcomes. The use of a commonly agreed upon definition of psychological pain will enhance knowledge development that, ultimately, can benefit assessment and treatment of individuals who experience psychological pain.

Chapter 2

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Three

Brain Regions Associated with Psychological Pain: Implications for a Neural Network and its Relationship to Physical Pain

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Chapter 3

Psychological pain may be as old as human self-awareness, but it remains immature as a concept in that its unique nature and complexities are minimally understood. Unlike physical pain it has received little attention in studies of the brain (Biro, 2010). Research on physical pain is abundant and the network of brain areas involved in such pain is well described (Apkarian, Bushnell, Treede, & Zubieta, 2005; Hudson, 2000; Schnitzler & Ploner, 2000). Similarly, brain areas involved in emotions (e.g. sadness, happiness, anger, fear, disgust) are well studied and comprehensively reviewed (Davidson & Irwin, 1999; Phan, Wager, Taylor, & Liberzon, 2002; Wager, Phan, Liberzon, & Taylor, 2003). However, none of these reviews have addressed psychological pain.

Mee, Bunney, Reist, Potkin, and Bunney (2006) were the first to suggest specific brain areas that may play a role in psychological pain. Based on a review of studies on grief, social exclusion, and induced sadness, they concluded that brain areas involved in psychological pain overlap with the physical pain network, particularly the insula, prefrontal cortex (PFC), and anterior cingulate cortex (ACC). Only the somatosensory cortices were uniquely activated in physical pain. While other authors have also suggested that psychological pain and physical pain use similar areas of the brain (Biro, 2010; Macdonald & Leary, 2005), this assertion has been based on a variety of studies that did not assess actual psychological pain. A further limitation of these studies is the large heterogeneity in methods used to evoke emotions, which included watching sad film clips, displaying sad photos or pictures, reading sad words or sentences, recalling sad events, and playing a game that involved exclusion.

Based upon analysis of the literature to date, psychological pain was defined as "a lasting, unsustainable, and unpleasant feeling resulting from negative appraisal of an inability or deficiency of the self" (Meerwijk & Weiss, 2011). This definition is the result of a synthesis of perspectives from existing concepts and theories of psychological pain. Psychological pain is a

lasting feeling in that it endures, it does not pass quickly and it takes time to resolve. One does not experience psychological pain for just a few seconds or minutes. Usually, it is hours, days, weeks, or even longer, although the intensity of the pain may vary during that period. Examples of situations that may cause psychological pain include a) the inability to protect oneself or a loved one from injury, disease, or embarrassment, b) feeling deficient because of a lack of love or affiliation, or because of lost autonomy due to a pervasive illness. The needs to love, be loved, to affiliate, and to avoid harm are core psychological needs that were described by Murray (1938/2008). In his theory of psychological pain, Shneidman (1998) has noted that frustration of psychological needs may cause unbearable psychological pain. Grief over losing a loved one, for example, represents a frustration of the need to love and be loved, and a frustration of the need to protect someone who is cared about deeply. Psychological pain is the result of negative appraisal of this inability or deficiency of the self.

Although psychological pain has the potential to foster personal growth and an enhanced sense of meaning, it has been associated to a greater extent with decreased mental well-being. In particular, it has been identified as a symptom in major depressive disorder (MDD) and as a precursor of suicide ideation and behavior (Chavez-Hernandez, et al., 2009; Mee, et al., 2011; Olié, et al., 2010; Orbach, et al., 2003a; Pompili, et al., 2008; Shneidman, 1998; Troister & Holden, 2010). In this sense, psychological pain is unsustainable in that it cannot be endured indefinitely without adverse consequences. Growing evidence points to the negative effects of poor mental health on physical health (Prince, et al., 2007; S. J. Weiss, et al., 2009). Thus, identification of brain areas involved in psychological pain may help guide development of interventions to decrease mortality and morbidity.

The purpose of this paper is to provide an up-to-date overview of studies on brain function related to psychological pain. This systematic review was limited to studies in which current psychological pain was

assessed and studies in which participants recalled an autobiographical sad event (e.g. loss of a close friend or family member, a relationship break-up), as this was assumed to evoke a mood state closer to actual psychological pain than externally generated methods (e.g. viewing sad pictures or films). Evidence indicates that recall of autobiographical events is an effective method of mood induction (Martin, 1990). Specific aims of the review were (a) to describe a potential brain network for psychological pain by identifying brain areas that are activated during the experience of psychological pain, and (b) to identify the extent of overlap between brain areas involved in psychological pain and physical pain.

Methods

Search Strategy

Medline was accessed for literature with search terms pertaining to psychological pain and brain function; publications were selected if they matched the combination of these terms. Because various alternatives are used in the literature to refer to psychological pain, a broad search strategy was used including terms like psychological pain, mental pain, emotional pain, psychic pain, and psychache. Publications that mentioned suicide, negative affect, or the combination of pain and emotions were also included as possibly pertaining to psychological pain, as were articles that mentioned suffering, anguish, or torment in the title. Search terms pertaining to brain function included brain, brain function, brain activity, and brain mapping. Combination of the search terms for psychological pain and brain function resulted in 1335 hits up to the publication year 2011, while excluding reviews and limiting to articles on humans published in English.

After assessing the titles for applicability, 128 articles remained of which the abstracts were read. Based on these abstracts, another 73 articles

were excluded because they (a) did not report results of a neuroimaging study, (b) reported on simulated, imagined or anticipated nociceptive pain or an affective response to a real nociceptive pain stimulus, (c) reported on an affective response other than psychological pain (e.g. fear, anger, anxiety, aversion) or the affective response was unknown, and (d) did not fit our established definition of psychological pain. The remaining 55 articles were obtained, and another 10 articles were identified via reference lists. As a final limitation, unless they specifically assessed psychological pain, studies were excluded if they did not use a significant autobiographical event to reexperience the sad mood state associated with that event. This left 18 articles that could be used for this review. Use of these criteria aimed to comprise a more homogeneous set of studies so that the analysis would not be confounded by vastly different methods or definitions of psychological pain.

Analysis

If studies reported nonspecific labels to refer to brain areas (e.g. occipital cortex rather than a more specific subregion like cuneus or lingual gyrus), either the reported Brodmann area ([BA], Strotzer, 2009) or Talairach coordinates (Talairach & Tournoux, 1988) were used to find a more specific label with the Talairach client software developed by the International Consortium for Brain Mapping (Lancaster, et al., 1997; Lancaster, et al., 2000). If coordinates were reported in the Montreal Neurological Institute reference system (Collins, Neelin, Peters, & Evans, 1994), a conversion to Talairach space was carried out using the BrainMap software developed by the Research Imaging Institute, University of Texas Health Science Center San Antonio (Eickhoff, et al., 2009). To facilitate interpretation, all reported labels referring to the PFC (e.g. orbitofrontal cortex, frontal gyri) were relabeled as Brodmann areas 8 – 11 or 44 – 47, using the aforementioned software tools.

A pragmatic stance was taken to focus on brain regions for which at least three studies reported activation, regardless of whether other studies had reported deactivation, or vice versa. A difference of three in observed frequency corresponds to a $\chi^2 > 10.827$ ($df = 1$, $p < .001$) under a null hypothesis that no activity change would be observed ($N = 18$). When activation differences were tested between two subsamples, Fisher's exact test was reported instead of χ^2 because Fisher's exact test is more appropriate when sample sizes and expected cell sizes are small (Munro, 2005). For those comparisons that did allow meaningful χ^2 analysis, built-in functions in Microsoft Excel® 2008 for Mac (version 12.2.7) were used. Fisher's exact test was performed in PASW Statistics® for Mac (version 18.0).

Results

Table 3.1 shows the general characteristics of 18 studies that met the criteria for this review. Indicative of a dearth of research on psychological pain and brain function, only two studies (Reisch, et al., 2010; van Heeringen, et al., 2010) were found that used actual measures to assess current psychological pain. The remaining studies assessed brain function in participants who experienced grief or who recalled grief ($n = 4$), or who recalled sadness ($n = 12$). Many of the studies had subjects recall how they felt after they had lost somebody close to them (e.g. a parent, sibling, spouse, baby). In other studies, subjects recalled break-up of a romantic relationship, and sometimes illness of a loved one was recalled.

Table 3.1 General characteristics of studies included in this review ($N = 18$).

Author	Year	Reference Condition	Gender	Design	Population	Mapping
		assessed psychological pain				
Reisch et al.	2010	neutral mood task	8f	w	attempted suicide	fMRI
van Heeringen et al.	2010	low psychological pain	17m/22f	b	MDD	SPECT
		current/recalled grief				
Kersting et al.	2009	neutral mood task	24f	b	healthy	fMRI
O'Connor et al.	2008	neutral mood task	23f	b	healthy	fMRI
Najib et al.	2004	neutral mood task	9f	w	healthy	fMRI
Gündel et al.	2003	neutral mood task	8f	w	healthy	fMRI
		recalled sadness				
Keedwell et al.	2005	neutral mood task	8m/16f	b	MDD & healthy	fMRI
Markowitsch et al.	2003	eyes fixed task	6m/7f	w	healthy	fMRI
Pelletier et al.	2003	neutral mood task	5m/4f	w	healthy	fMRI
Zubieta et al.	2003	relaxed state	14f	w	healthy	PET
Liotti et al.	2002	relaxed state	25f	w	MDD & healthy	PET
Damasio et al.	2000	neutral mood task	11m/14f	w	healthy	PET
Liotti et al.	2000	neutral mood task	8f	w	healthy	PET
Lane et al.	1997	neutral mood task	12f	w	healthy	PET
Gemar et al.	1996	neutral mood task	11m	w	healthy	PET

Author	Year	Reference Condition	Gender	Design	Population	Mapping
George et al.	1996	neutral mood task	10m	w	healthy	PET
George et al.	1995	neutral mood task	11f	w	healthy	PET
Pardo et al.	1993	relaxed state	4m/3f	w	healthy	PET

Note. b: between subjects, f: female, fMRI: functional magnetic resonance imaging, m: male, MDD: major depressive disorder, PET: positron emission tomography, SPECT: single photon emission computed tomography, w: within subjects. Gender column indicates gender and number of participants.

Among the results of our search strategy were studies on social pain that resulted from social exclusion (Eisenberger, Lieberman, & Williams, 2003; Onoda, et al., 2009). Although, these studies fit our definition of psychological pain (social exclusion represents a frustration of the need to affiliate, which is an inability of the self that is negatively appraised), we did not include them in our review because they employed an experimental manipulation, rather than a real-life autobiographical event that caused the social pain. One more study (Schmahl, Vermetten, Elzinga, & Bremner, 2004) that fit our definition of psychological pain (subjects recalled childhood abuse) was not included because the mood state that resulted from recall was not only sadness but could also have involved fear and anger.

A complete overview of brain regions that showed increased or decreased activity is shown in Table 3.2 at the end of this chapter. Figure 3.1 shows a summary of that table based on brain regions for which three or more studies reported activation or deactivation. Figure 3.1 distinguishes brain areas within three broad areas: the left and right hemispheres and the medial subcortical area.

Reported brain activity in all studies was based on the subtraction method (Friston, et al., 1995), in which values for brain imaging variables (e.g. cerebral blood flow, blood oxygen level dependency) in a reference condition were subtracted from values obtained during an experimental condition or values in a population of interest. The experimental condition involved such tasks as listening to or reading scripts of painful autobiographical events (e.g. illness or death of a loved one, suicidal behavior) and recalling a memory or displaying faces of lost loved ones. In the majority of studies, the reference condition involved a task to evoke a neutral mood that was similarly structured as the task that involved reexperiencing psychological pain, grief, or extreme sadness. Only four studies did not use a specific task as a reference (see Table 3.1).

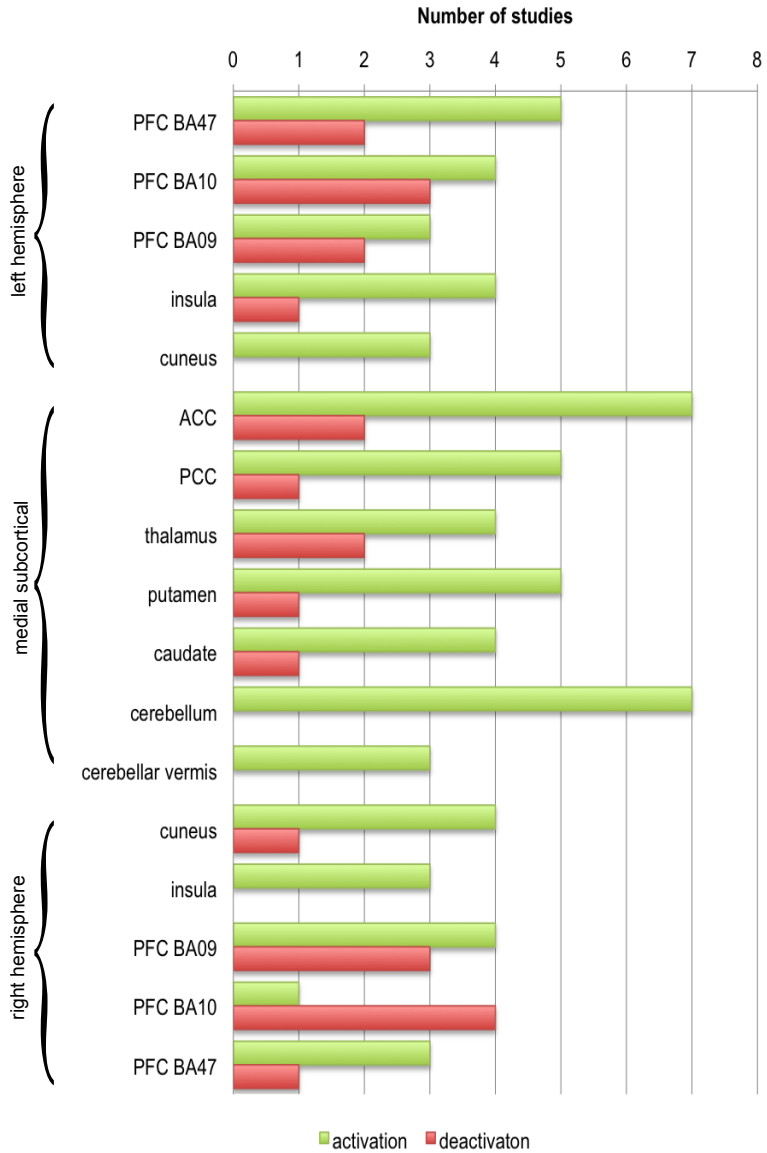


Figure 3.1 Brain areas that showed activity change in response to psychological pain (including the grief and recalled sadness subsamples) for which three or more studies showed activation or deactivation ($N = 18$). BA: Brodmann area, ACC: anterior cingulate cortex, PCC: posterior cingulate cortex, PFC: prefrontal cortex.

Studies Involving Assessed Psychological Pain

Van Heeringen et al. (2010) examined the effect of psychological pain severity on resting state activity in patients with major depressive disorder (MDD) by comparing patients who scored high in psychological pain to those who scored low. In addition to effects on brain activity as detailed in Table 3.2, psychological pain was positively correlated with hopelessness (r_s = .517, $p < .001$) and suicide ideation (r_s = .425, $p < .05$). Reisch et al. (2010) tested the hypothesis that negative emotions experienced as psychological pain would exhibit decreased neural activity in the frontal cortex. Their sample included women who had attempted suicide in the two months prior to the study. Both studies found increased activity in the right cuneus, but apart from that no consistent findings were evidenced across the two studies. Reisch et al. reported decreased PFC activity (left BA46, right BA10), whereas van Heeringen et al. reported increased activity in the right PFC (BA9, BA44). It should be noted that different reference conditions were used. Both studies used the Orbach & Mikulincer Mental Pain questionnaire to assess psychological pain, which has been shown to be reliable and have a high degree of validity (Orbach, et al., 2003b; Soumani, et al., 2011; van Heeringen, et al., 2010).

Studies Involving Grief

All four studies that reported on grief-related brain activity were conducted in otherwise healthy women. Najib et al. (2004) studied women who ruminated over a romantic relationship that ended during the 4 months prior to the study, and O'Connor et al. (2008) studied women who had lost a mother or sister to breast cancer during the past 5 years. Gündel et al. (2003) used a sample of women who had lost a first-degree relative (father, mother, or husband) during the past 12 months. Kersting et al. (2009) compared

women who had lost a preterm baby after induced labor during the past 2 months to women who delivered a healthy baby during the past 12 months.

A common finding in three of the four studies was increased activity in the left cuneus and posterior cingulate cortex (PCC) during grief. Two of the four studies found increased activity in the left lingual gyrus, the cerebellum and right middle temporal gyrus (for details see Table 3.2). Conflicting results were reported for the left BA10, BA47, inferior temporal gyrus, nucleus accumbens, the thalamus, ACC, and the right BA47 and lingual gyrus. Striking was the relatively large number of deactivated brain areas reported by Najib et al. (2004)

Studies Involving Recalled Sadness

As shown in Table 3.1, twelve studies reported on changes in brain activity due to recalled sadness, almost half of which focused exclusively on women and two studies included men only. One study had a mixed-gender sample (Pardo, Pardo, & Raichle, 1993), but reported results for male and female participants separately, which were therefore included as separate entries in Table 3.1. All studies involved healthy participants and two studies included a comparison with patients with unipolar depression (Liotti, Mayberg, McGinnis, Brannan, & Jerabek, 2002) or MDD (Keedwell, Andrew, Williams, Brammer, & Phillips, 2005). The study by Pelletier et al. (2003) was remarkable because they used professional actors for their ability to self-induce and experience powerful emotional states.

While focusing on brain areas that were reported by at least three studies, evidence for increased activity during recalled sadness was most convincing for the caudate (5 studies), the left insula, cerebellum, and putamen (4 studies), and the right insula (3 studies). Conflicting results were reported for the left BA9, BA10, BA47, the ACC, PCC, and thalamus, and the right BA9, BA10, and BA11.

Discussion

Under the null hypothesis that brain activations and deactivations would be equally frequent, this review found a significant difference between the overall numbers of activations versus deactivations associated with psychological pain. Across all studies ($N = 18$), increased activity was reported 111 times (see Table 3.2), whereas decreased activity was reported 73 times ($\chi^2 = 7.85$, $df = 1$, $p = .005$). When comparing increased activity versus decreased activity for the left and right hemispheres, and medial subcortical area separately, only the medial subcortical area showed significantly more activation than deactivation across all studies (47 increases vs. 15 decreases, $\chi^2 = 16.51$, $df = 1$, $p < .0001$). It should be noted that two studies did not report on brain deactivations (Gündel, et al., 2003; Lane, Reiman, Ahern, Schwartz, & Davidson, 1997). Moreover, decreased brain activity assessed through cerebral blood flow and blood oxygen level dependency should be interpreted with caution. As the amount of blood available to the brain is approximately constant (Sergent, 1994), an increase in blood volume in one region is necessarily accompanied by a decrease of blood in another region, and as such decreased brain activity may be unrelated to a specific brain function at that exact moment.

Despite the fact that this review included studies that were relatively homogeneous with respect to the evoked emotion and mood induction method (recall of autobiographical life events), considerable variation exists in study outcomes. Disregarding any variation in study designs and populations, it is clear from Figure 3.1 that no one brain region was activated in all studies. Changes in brain activity were not reported by more than 47.4% of the studies for any brain region, which is not an uncommon outcome: Mee et al. (2006) found that the most frequently implicated brain areas showed activity changes in 47.8% of the studies, and an extensive meta-analysis of human brain activity studies on emotion

(Phan, et al., 2002) reported a maximum support in 62% of the studies. The latter meta-analysis did not distinguish between left and right hemispheres, which may have contributed to the higher percentage of agreement.

Among the limitations of this review is the relatively small number of included studies ($N = 18$). Therefore, interpretations should be considered tentative, especially where subsamples are compared. Studies involved primarily healthy study populations, but also people who had been diagnosed with depression and people who had attempted suicide. Although a psychological pain experience is what connected all studies, the presence of depression and suicidal thoughts in some subjects may have had a confounding effect. However, suicidality and depression are conditions that are well known for a high level of psychological pain (Mee, et al., 2011; Olié, et al., 2010; Reisch, et al., 2010) so it would seem inappropriate to exclude those studies. In the following discussion, we use the term 'psychological pain' to refer to the broader concept and in reference to all studies that were included in the review. In discussions of differences between subsamples, we use 'assessed psychological pain' in reference to the subsample of studies that used actual measures of psychological pain to distinguish them from the grief and recalled sadness subsamples.

Brain Areas Involved in Psychological Pain

Figure 3.1 suggests that the evidence for involvement of brain areas in psychological pain is most convincing for the medial subcortical area. Medial brain areas that were most consistently implicated are the ACC, PCC, thalamus, basal ganglia (putamen and caudate), cerebellum and the cerebellar vermis. These areas all predominantly showed activation, with the ACC and cerebellum receiving the greatest support across studies. The involvement of the ACC in negative emotion has been well established (Bush, Luu, & Posner, 2000; Davidson & Irwin, 1999). A more recent review

(Vogt, 2005) suggested that the subgenual ACC is involved in the experience of sadness in particular, and recently the anterior midcingulate cortex was identified with a control function for both negative affect and physical pain (Shackman, et al., 2011). Although Phan et al. (2002) found the cerebellum to be involved in emotion, it is not typically associated with emotion. However, evidence for a connection between the cerebellum and negative affect is steadily growing (Borsook, Moulton, Tully, Schmahmann, & Becerra, 2008; Colibazzi, et al., 2010; Moulton, et al., 2011; Schmahmann, 2004; Wolf, Rapoport, & Schweizer, 2009). Our findings also showed activation of the medial part of the cerebellum, the cerebellar vermis, during grief and recalled sadness. As this part of the cerebellum is believed to be involved in proprioception and perception of self-motion (Yakusheva, et al., 2007), it is as yet unclear how this effect relates to psychological pain. Earlier reviews on pain and emotion (Apkarian, et al., 2005; Phan, et al., 2002) did not distinguish the cerebellar vermis from the lateral parts of the cerebellum.

With respect to the left and right hemispheres, the bilateral insula also showed cogent evidence for activation. The PFC is among the most frequently implicated areas in this review, in particular BA 9, 10, and 47, but the direction of the activity change is not clear. There appears to be support for bilateral increased activity in the lateral PFC (BA 47). In both the left and right dorsomedial PFC (BA 9), however, the number of studies indicating increased versus decreased activity differs by only one. Bidirectional evidence also exists for the left ventromedial PFC (BA 10), whereas the right ventromedial PFC convincingly shows decreased activity. Right-sided decreased activity is opposite of what was previously found (Sackeim, et al., 1982; Tucker, 1981). An inverse correlation between medial PFC activity and arousal was recently reported (Gerber, et al., 2008), which suggests that decreased right ventromedial PFC activity may reflect increased arousal during psychological pain.

Drevets and Raichle (1998) found reciprocal behavior between lateral and medial PFC areas during intense emotion and suggested a more prominent role of the *medial* PFC in emotion processing (e.g. appraisal of emotion) while neural activity was suppressed in cognitive processing areas (lateral PFC). After collapsing our findings for the PFC into lateral (BA 44 – 47) and medial (BA 8 – 11) areas, this review found no evidence of reciprocal behavior in the left PFC (both lateral and medial PFC showed increased activity), and only weak evidence for reciprocal behavior in the right PFC, most prominently between BA10 and BA47 (see Figure 3.1). In fact, the evidence contradicts Drevets and Raichle's findings (1998) in that it suggests increased activity in the lateral PFC during psychological pain. Our findings are in line with those of Nielen and colleagues (2009) who provide evidence that bilateral activation of the lateral PFC is associated with negative affect. According to Phan et al. (2002), the medial PFC is commonly activated across emotions, and this was found to be true to a much lesser extent for the lateral PFC. It should be noted that the meta-analysis by Phan et al. (2002) did not take decreased brain activity into account. However, even when ignoring decreased brain activity, our findings do not show a clear difference in involvement between lateral and medial PFC areas in psychological pain.

This review also found convincing evidence for increased activity in the cuneus. However, as noted in one of the reviewed studies (Najib, et al., 2004), the cuneus is involved in visual processing, and activation of this region could be the result of more vivid imagery during recall of the psychological pain than of the pain per se. Three of the six studies (George, Ketter, Parekh, Herscovitch, & Post, 1996; Gündel, et al., 2003; Kersting, et al., 2009) that reported increased activity in the cuneus had a visual component as part of their experimental manipulation, and two studies included a recall phase (Najib, et al., 2004; Reisch, et al., 2010). Moreover,

Phan et al. (2002) found a significant effect of visual mood induction methods on occipital cortex activation.

Assessed Psychological Pain and Grief versus Sadness

Comparison of activity changes between the subsamples (assessed psychological pain, grief, recalled sadness) showed that most affected brain regions were found across the subsamples, providing support for the assumption that grief and extreme sadness are similar emotions or affective states to what would be considered psychological pain in the strictest sense. It is noteworthy, however, that all studies that observed increased activity in the insula, putamen and caudate were in the sadness subsample (see Table 3.2).

Colibazzi et al. (2010b) found evidence for activation of the parahippocampal gyrus (PHCG) during highly arousing emotions. In our review, activation of the PHCG was reported by two studies, neither of which was in the recalled sadness subsample, which suggests that subjects in the recalled sadness subsample may have experienced less arousal than those in the grief and assessed psychological pain subsample. Treating the assessed psychological pain and grief subsample as one group and testing the number of PHCG activations for differences with the recalled sadness subsample approached significance for activation during grief/assessed psychological pain (Fisher's exact test, $p = .058$).

Taken together, these comparisons between subsamples show overlap in affected brain areas. However, as evidenced by brain areas that are uniquely activated during recalled sadness or in the grief/assessed psychological pain subsample only, grief may be a more accurate exemplar of psychological pain than recalled sadness.

CHAPTER 3

Psychological Pain versus Physical Pain

Apkarian et al. (2005) described the brain network for physical pain, based on a meta-analysis of studies that used hemodynamic, neuroelectrical, or neurochemical methods. They concluded that the most important components of the pain network in the brain were the insula, ACC, PFC, thalamus, and the primary and secondary somatosensory cortices. These areas were consistently implicated across modalities of pain (various types of induced pain and pain in clinical settings) and modalities of imaging (e.g. PET, fMRI). Areas that were less consistently implicated were the amygdala, cerebellum, basal ganglia, PCC, posterior parietal cortex, and motor cortices.

Comparing the findings of our review, as indicated in Figure 3.1, with the brain areas involved in physical pain shows an overlap with the main pain network, in particular the insula, ACC, PFC and thalamus. Overlap is also observed in secondary areas, in particular the cerebellum, basal ganglia (putamen, caudate), and PCC. A striking difference is that our review found the PCC to be involved in 31.6% of the studies, whereas Apkarian et al. (2005) found it was involved in about 9% of the physical pain studies. This suggests a more prominent role of the PCC in psychological pain. Activation of the PCC was also found in almost 40% of studies on emotion (Phan, et al., 2002), specifically fear, sadness, and happiness. Hudson (2000) stated that the PCC has an evaluative role, and Vogt (2005) suggested that the PCC, especially the ventral part, serves the purpose of assessing self-relevance of emotional events. These observations provide corroborating evidence for an appraisal function as an essential component of the psychological pain concept (Meerwijk & Weiss, 2011). Our findings also indicate that the cerebellum may play a more prominent role in psychological pain than in physical pain. It was one of the brain regions most

consistently activated in our review but appeared to be less consistently implicated in Apkarian's results.

Phan et al. (2002) found that almost 60% of studies that used recall to induce emotion reported activation of the insula. As all but one (van Heeringen, et al., 2010) of the studies included in our review involved recall of autobiographical events, it is interesting that our review showed activation of the insula in sadness studies only. With respect to physical pain, evidence was provided that the insula is activated in acute pain and less so during chronic pain (Apkarian, Baliki, & Geha, 2009; Apkarian, et al., 2005). Taken together, absence of insular activation during psychological pain may indicate an enduring condition that is more similar to chronic pain.

Involvement of the PFC in both psychological pain and physical pain deserves more detailed attention, as Apkarian et al. (2005) presented convincing evidence of PFC activation in physical pain. Although the PFC was implicated by many studies in this review, the results for PFC involvement in psychological pain were not entirely consistent. The PFC area that does appear to be activated in psychological pain is the lateral PFC (BA 47). We found convincing evidence for *decreased* activity in the right BA 10, whereas results for the left BA 10 and bilateral BA 9 were only slightly in favor of increased activity. The PFC in general is thought to be involved in cognitive, emotional, and memory functions (Apkarian, et al., 2005). Specifically, the ventromedial PFC (BA 10) was suggested to be involved in the representation of positive and negative emotional states (Davidson & Irwin, 1999). However, others have ascribed it a role in planning and reasoning (Hudson, 2000).

The following brain areas that were implicated in physical pain, did not reach our pragmatic threshold of support by at least three studies: amygdala, posterior parietal cortex, motor cortices, and the primary and secondary somatosensory cortices. However, it should be noted that all these areas showed activation or deactivation in one or two studies (see Table 3.2).

A likely explanation for lack of consistent activation of the motor and somatosensory cortices is the absence of a nociceptive stimulus in psychological pain. The posterior parietal cortex is predominantly involved in planned movement. As such it may have a role in avoiding a painful stimulus. Since there is no stimulus in psychological pain that may be avoided by movement, it is likely that the posterior parietal cortex is not involved in psychological pain. An interesting finding is lack of activation of the amygdala in this review. None of the studies reported activity changes in the right amygdala, and only two studies (Najib, et al., 2004; Zubieta, et al., 2003) reported *decreased* activity in the left amygdala. The amygdala is thought to be involved in evaluating emotional importance of stimuli and appears to be especially active in response to fear (Phan, et al., 2002). About 7% of studies in the meta-analysis by Apkarian et al. (2005) reported involvement (both activation and deactivation) of the amygdala in physical pain, which may be attributed to some level of fear due to being subjected to a painful stimulus. The lack of amygdala activity in our review could, to some extent, reflect the fact that fear was not a key element of the studies that were included. In addition, the amygdala has been described as a salience and ambiguity detector in response to external stimuli (Gerber, et al., 2008). This neural function may not be as relevant to the processing of internal feelings for which salience may already have been established and ambiguity is not an issue.

Conclusions

This systematic review compared changes in brain activity during the experience of psychological pain. Only two studies that included a measure of actual psychological pain were identified for this review, which included 18 studies in total. Four studies involved current or recalled grief, and 12 studies involved recalled sadness. The latter 16 studies were included because they used a significant autobiographical event to induce a sad mood

state and fit the definition of psychological pain that was established for the study. Prior to this review it was assumed that brain function in grief and sadness could be used as proxies of psychological pain (Mee, et al., 2006). Although the number of studies included in this review was too small to allow statistical testing between subsamples for most comparisons, the evidence suggests that brain regions associated with actual measurement of psychological pain may be more similar to those involved in grief than to those involved in recalled sadness. The PHCG was found to be activated in two studies: one where psychological pain was assessed (Reisch, et al., 2010) and the other involving grief (Najib, et al., 2004). In contrast, activation of the insula, caudate and putamen was only observed in the sadness studies. As PHCG activation was related to greater arousal (Colibazzi, et al., 2010), these findings suggest that psychological pain may be more intense than recalled sadness, and possibly reflect a higher level of arousal. In line with our earlier definition of the concept, grief may be a clear instance of psychological pain.

The central question in this review was about which brain areas are involved in the experience of psychological pain. Taking into account the potential differences between psychological pain and sadness, the following brain areas are most likely activated during the experience of psychological pain: ACC, PCC, thalamus, cerebellum, and PHCG. Implications for the PFC (BA 9, 10, and 47), with the exception of bilateral BA 47 (activated) and right BA 10 (deactivated), are less conclusive because the number of studies that reported activation and deactivation differed by only one. Based on these observations, the following tentative psychological pain network is proposed (see Figure 3.2). Initially, the thalamus processes and relays information related to psychological pain from the various sensory systems to corresponding cortical areas (Hudson, 2000). The medial thalamus projects to the ACC, which may play a central role in the affective (unpleasant feeling) component of psychological pain. Bidirectional communication exists between

the ACC and the PCC (Price, 2000), with the PCC possibly involved in evaluating the self-relevance (appraisal component) of psychological pain. In fact, functional connectivity analysis has revealed a significant correlation between cortical activity in the ventral PCC and ACC during evocation of grief (M. F. O'Connor, Gündel, McRae, & Lane, 2007). The PFC is also bidirectionally connected to the ACC (Price, 2000) and may serve a memory and planning function during acute psychological pain as well as enduring psychological pain. Furthermore, right ventromedial PFC activity was related to the parasympathetic nervous system (Hilz, et al., 2006; Tanida, et al., 2004), which is generally thought to represent inhibition (Sherwood, 2010). As our review found predominant deactivation of the right ventromedial PFC (BA10), this provides additional support for greater arousal during psychological pain. Bidirectional communication exists between the PFC and the cerebellum (Ramnani, 2006; Schmahmann & Pandya, 1997). The cerebellum has traditionally been associated with motor coordination; however, more recently evidence has emerged regarding its affective role (Wolf, et al., 2009), especially in mediating negative emotion (Colibazzi, et al., 2010). Moreover, research indicates that the cerebellum modulates the emotional and cognitive experience of physical pain (Borsook, et al., 2008), a function it may serve in psychological pain as well. The cerebellum is also connected to paralimbic structures (Schmahmann & Pandya, 1997), among which is the PHCG that may have a memory function, especially for negatively valenced and more arousing memories (Kilpatrick & Cahill, 2003). As brain areas are involved in multiple functions, we do not suggest that the brain areas implicated in the proposed neural network are solely dedicated to the experience of psychological pain. Additional research (e.g. functional connectivity analysis) is needed to confirm the components of this proposed network for psychological pain and further clarify their individual roles in the experience of psychological pain.

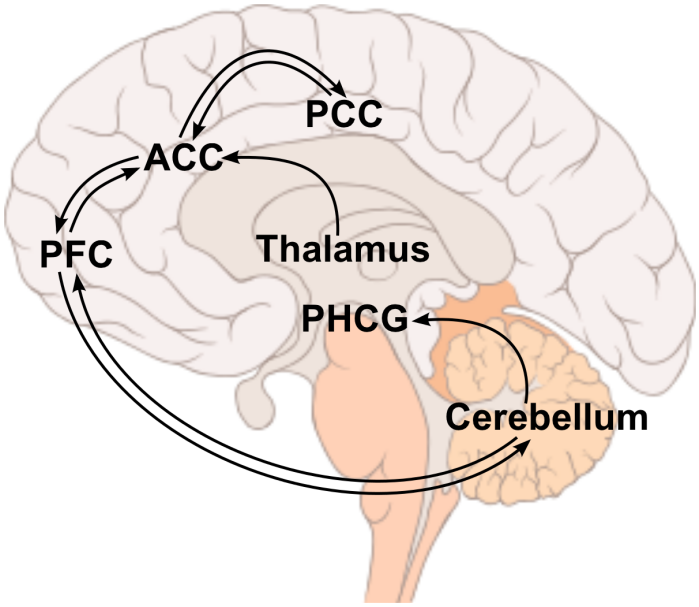


Figure 3.2 Schematic of tentative neural network involved in psychological pain. ACC: anterior cingulate cortex, PCC: posterior cingulate cortex, PFC: prefrontal cortex, PHCG: parahippocampal gyrus. (Original source, http://commons.wikimedia.org/wiki/File:Brain_bulbar_region.svg, modified with permission).

A final question for this review concerned the comparison of brain areas involved in psychological pain and physical pain. The proposed neural network for psychological pain (see Figure 3.2) indicates a partial overlap with the pain network identified by Apkarian et al. (2005): ACC, thalamus, PFC, PCC, and cerebellum. Whether the overlap extends to the bilateral insula, as suggested by Mee et al. (2006) and basal ganglia (putamen, caudate) requires further research, as these areas did not show activation in studies of psychological pain proper or grief. Lack of activation in the amygdala, posterior parietal cortex, motor cortices, and primary and secondary somatosensory cortices is most likely due to absence of a nociceptive stimulus in the studies that were included. Additional research is

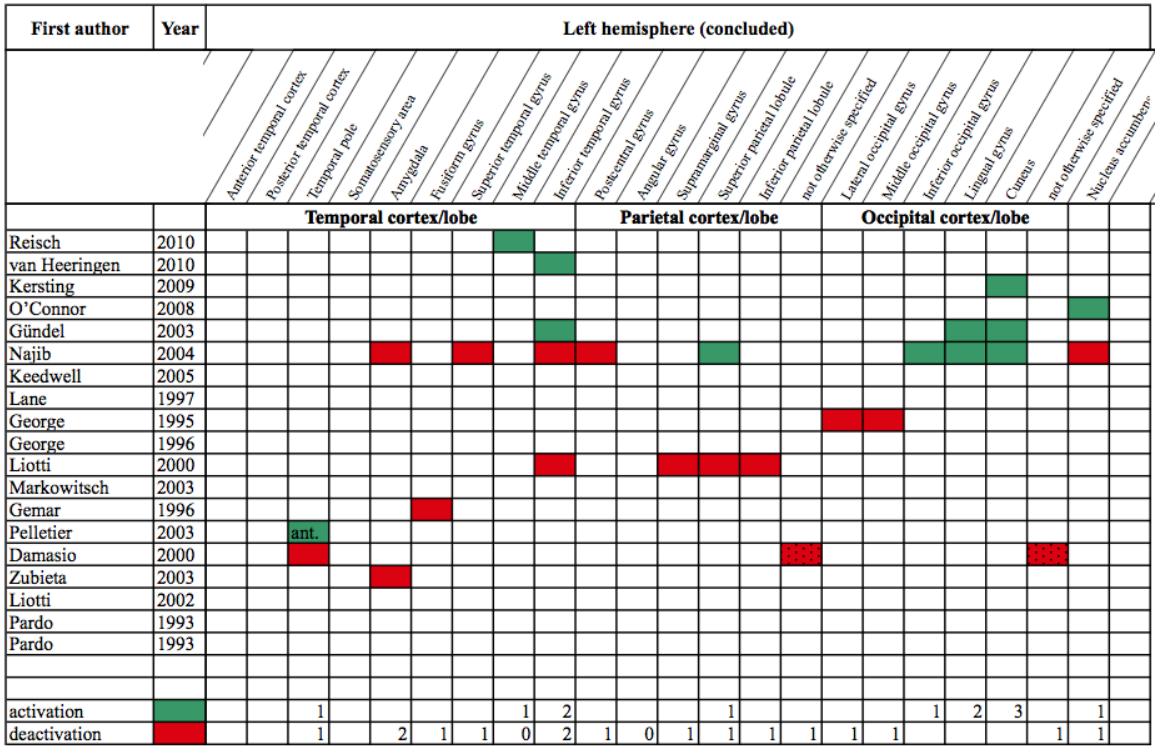
required to confirm the more frequent activation of the PCC, compared to physical pain, as found in this review. Moreover, additional research may find that subregions of the PFC behave differently in psychological pain and physical pain, as the PFC is a relatively large and heterogeneous area (Apkarian, et al., 2005).

Millions of people worldwide may experience psychological pain, and enduring psychological pain may result in decreased mental well-being, pathology, and potentially suicide. Knowledge about brain functioning that underlies the experience of psychological pain can guide development of psychosocial and pharmacological therapies to alleviate psychological pain.

Table 3.2 Brain areas in which activity changes occurred during the experience of psychological pain.

The following table shows areas of changed brain activity during the experience of psychological pain, as implicated by 18 studies included in this review. Results for each study are shown for the study condition in which higher intensity of psychological pain was expected (e.g. higher vs. lower psychological pain, complicated grief vs. noncomplicated grief, sadness vs. neutral mood). The brain areas are non-overlapping and organized under the left and right hemispheres and subcortical medial areas. Green cells in the table indicate increased activity and red cells indicate decreased activity. Dotted cells indicate that a study reported a global brain area, whereas other studies may have distinguished subdivisions.

First author	Year	Paradigm	Gender	Left hemisphere													
					Inferior frontal gyrus	BA 47	BA 46	BA 45	BA 44	BA 11	BA 10	BA 9	BA 8	Premotor cortex	Motor cortex	Anterior insula	Posterior insula	
					Frontal cortex/lobe											Insula		
Reisch	2010	assessed PP	f															
van Heeringen	2010	assessed PP	f/m															
Kersting	2009	grief	f															
O'Connor	2008	grief	f															
Gündel	2003	grief	f															
Najib	2004	grief	f															
Keedwell	2005	sadness	f/m															
Lane	1997	sadness	f															
George	1995	sadness	f															
George	1996	sadness	m															
Liotti	2000	sadness	f															
Markowitsch	2003	sadness	f/m															
Gemar	1996	sadness	m															
Pelletier	2003	sadness	f/m															
Damasio	2000	sadness	f/m															
Zubieta	2003	sadness	f															
Liotti	2002	sadness	f															
Pardo	1993	sadness	f															
Pardo	1993	sadness	m															
activation						5				1	4	3	1	2		4		
deactivation						2	2	1	1	1	3	2	1	1	1	1		


First author
Year
Left hemisphere (concluded)
Anterior temporal cortex
Posterior temporal cortex
Temporal pole
Somatosensory area
Amygdala
Fusiform gyrus
Superior temporal gyrus
Middle temporal gyrus
Inferior temporal gyrus
Postcentral gyrus
Angular gyrus
Supramarginal gyrus
Superior parietal lobule
Inferior parietal lobule
not otherwise specified
Lateral occipital gyrus
Middle occipital gyrus
Inferior occipital gyrus
Lingual gyrus
Cuneus
not otherwise specified
Nucleus accumbens
Temporal cortex/lobe
Parietal cortex/lobe
Occipital cortex/lobe
Reisch 2010
van Heeringen 2010
Kersting 2009
O'Connor 2008
Gündel 2003
Najib 2004
Keedwell 2005
Lane 1997
George 1995
George 1996
Liotti 2000
Markowitsch 2003
Gemar 1996
Pelletier 2003
ant.
Damasio 2000
Zubieta 2003
Liotti 2002
Pardo 1993
Pardo 1993
activation 1 1 2 1 0 2 1 0 1 1 1 2 3 1
deactivation 1 2 1 1 1 0 1 1 1 1 1 1 1

First author	Year	Medial brain																												
		Putamen	Caudate	Pallidum	Medulla	Anterior pons	Posterior pons	Midbrain	Paracentral lobule	Periaqueductal grey	ACC collapsed	Dorsal ACC	Middle ACC	Ventral ACC	Posterior cingulate cortex	Thalamus	Hypothalamus	Hippocampus	Parahippocampal gyrus	Uncus	Subcallosal gyrus	Cerebellum	Vermis	Precuneus						
		Basal ganglia			**Brainstem**						**Limbic system**																			
Reisch	2010																	R												
van Heeringen	2010				L																									
Kersting	2009								R				B		L	L														
O'Connor	2008																													
Gündel	2003														L															
Najib	2004					L	R				B				Bg	L	L		L	L	R	B		B						
Keedwell	2005														L															
Lane	1997	B	L					B								B	R					later	R							
George	1995	R														L														
George	1996	L	R												R															
Liotti	2000													L								post.	R							
Markowitsch	2003	R									R											medial								
Gemar	1996																													
Pelletier	2003						B																							
Damasio	2000	R		B		L		B							Ri	L						mesial	B							
Zubieta	2003			R																L										
Liotti	2002										B					ant.														
Pardo	1993																													
Pardo	1993																													
activation		5	4	1		1	2	2	1	1	7				5	4	1		2			7	3	1						
deactivation		1	1	2	1	1					2				1	2	1			2	1									

First author	Year	Right hemisphere																										
			Nucleus accumbens	not otherwise specified	Cuneus	Lingual gyrus	Inferior occipital gyrus	Middle occipital gyrus	Lateral occipital gyrus	not otherwise specified	Inferior parietal lobule	Superior parietal lobule	Supramarginal gyrus	Angular gyrus	Postcentral gyrus	Inferior temporal gyrus	Middle temporal gyrus	Superior temporal gyrus	Fusiform gyrus	Amygdala	Somatosensory area	Temporal pole	Posterior temporal cortex	Anterior temporal c	
			Occipital cortex/lobe							**Parietal cortex/lobe**						**Temporal cortex/lobe**									
Reisch	2010																								
van Heeringen	2010																								
Kersting	2009																								
O'Connor	2008																								
Gündel	2003				sup																				
Najib	2004																								
Keedwell	2005																								
Lane	1997																								
George	1995																								
George	1996																								
Liotti	2000																								
Markowitsch	2003																								
Gemar	1996																								
Pelletier	2003																								
Damasio	2000																								
Zubieta	2003																								
Liotti	2002																								
Pardo	1993																								
Pardo	1993																								
activation				4	2	1	1							1		2	1	1							
deactivation		1	1	1	2		1		1			1				1	1			1	1				

First author	Year	Right hemisphere (concluded)																	
		-cortex	Posterior insula	Anterior insula	Motor cortex	Premotor cortex	BA 8	BA 9	BA 10	BA 11	BA 44	BA 45	BA 46	BA 47	Inferior frontal gyrus				
		Insula			**Frontal cortex/lobe**														
Reisch	2010																		
van Heeringen	2010																		
Kersting	2009																		
O'Connor	2008																		
Gündel	2003																		
Najib	2004																		
Keedwell	2005																		
Lane	1997																		
George	1995																		
George	1996																		
Liotti	2000																		
Markowitsch	2003																		
Gemar	1996																		
Pelletier	2003																		
Damasio	2000																		
Zubieta	2003																		
Liotti	2002																		
Pardo	1993																		
Pardo	1993																		
																total	*left*	*right*	*middle*
activation		3		1	1		4	1	2	1	2		3	1		111	32	32	47
deactivation				1	1		3	4	2	1		1	1			73	32	26	15

Four

Reduced Midfrontal EEG Activity and Relative Left Complexity During Psychological Pain

CHAPTER 4

The traditional model of affect treats human emotion along two dimensions, representing various degrees of positive and negative emotions (Watson & Tellegen, 1985). Emotions like fear, sadness and happiness have been studied extensively in the brain (Wager, et al., 2003). While Wager et al. did not find evidence of overall lateralization of the brain during these emotions, results of studies in people with depression indicated relative right (greater right than left) frontal resting-state activity (Thibodeau, et al., 2006), in the alpha frequency range (8 – 13 Hz). This has become known as the valence model of affect, which considers positive emotions to be accompanied by relative left (greater left than right) frontal alpha activity, and negative emotions to be accompanied by relative right frontal alpha activity. Recent studies in people who had been diagnosed with major depressive disorder corroborated the findings of Thibodeau et al. (J. S. Chang, et al., 2012; Kemp, et al., 2010a), but null findings (Gold, Fachner, & Erkkila, 2012; Mathersul, et al., 2008), and contradicting results (E. Gordon, Palmer, & Cooper, 2010) were also reported.

The valence model of affect is generally accepted with respect to depression. However, research about anger and ostracism, or social rejection, suggests that the valence model may not generalize to all negative emotions. Anger, which is generally considered a negative emotion, has been shown to correspond with relative left frontal activity (Fairclough & Spiridon, 2012; Harmon-Jones, 2004; Herrero, Gadea, Rodriguez-Alarcon, Espert, & Salvador, 2010; Peterson, Gravens, & Harmon-Jones, 2011; Wacker, Heldmann, & Stemmler, 2003). Negative emotion in ostracism research may include both anger and sadness (Peterson, et al., 2011). These studies are in line with another model of affect called the motivational direction model of affect (Fox, 1991; Harmon-Jones, 2004), which distinguishes approach and withdrawal behavior, and states that approach behavior is accompanied by relative left frontal activity. Differences in study methodology should be taken into account. Contrary to most studies supporting the valence model of affect,

ostracism and anger studies were sometimes based on induced emotions, not on resting-state measurements. Indeed, anger was found to correspond with relative right frontal activity at rest (Jaworska, et al., 2012a), although relative left frontal activity at rest has also been reported (Harmon-Jones & Allen, 1998). Still others found asymmetry in frontal activity to depend on anger style (Hewig, Hagemann, Seifert, Naumann, & Bartussek, 2004; Stewart, Levin-Silton, Sass, Heller, & Miller, 2008).

As psychological pain is essentially an unpleasant feeling, the valence model of affect would suggest relative right (greater right than left) frontal alpha activity when people experience psychological pain, which would correspond with withdrawal behavior according to the motivational direction model of affect. On the other hand, psychological pain has been described as resulting from frustrated needs (Meerwijk & Weiss, 2011; Shneidman, 1998; Thornhill & Wilmsen Thornhill, 1989) and could be expected to result in approach behavior to have these needs fulfilled. The latter, according to the motivational direction model of affect, would suggest that people who experience psychological pain exhibit relative left (greater left than right) frontal alpha activity. A systematic review of brain imaging studies in people who experienced psychological pain or recalled a situation that was assumed to involve psychological pain, reported deactivation of the right medial prefrontal cortex (Meerwijk, Ford, & Weiss, 2013) during the experience of psychological pain. The result of that review likely reflects an outcome across the entire frequency range (total power), whereas support for the valence model and the motivational direction model was based on activity in the alpha frequency range specifically. If psychological pain follows the valence model of affect, the decrease in total power may be due to activity changes in frequency bands other than alpha.

Within the context of these models of affect, we aimed to (1) determine the direction of any association between psychological pain and resting-state frontal brain activity in standard EEG frequency bands, after

controlling for known covariates of psychological pain (depression, hopelessness, and suicide ideation), and (2) determine whether frontal EEG α-asymmetry predicts psychological pain, after controlling for covariates. As an exploratory aim of the study, the utility of the fractal dimension with respect to frontal EEG activity and psychological pain was studied.

Fractal dimension is a measure based on nonlinear dynamical systems theory (Shelhamer, 2007; Stam, 2006) and signifies dynamic complexity, capturing nonstationary changes in signal amplitude as well as frequency. In people with depression, fractal dimension of midfrontal EEG activity after electroconvulsive therapy has been shown to predict treatment response (Gangadhar, et al., 1999; Jagadisha, Gangadhar, Janakiramiah, Girish, & Ramakrishnan, 2003). Fractal analysis has also been shown to discriminate people with depression from healthy control subjects. Healthy people exhibited more complex spontaneous hand motion (Aybek, et al., 2012), and nonlinear measures like fractal dimension improved the ability to classify healthy people and people with depression (Hosseinifard, Moradi, & Rostami, 2013). In undergraduate students, significant associations between the fractal dimension of midfrontal EEG activity and self-focused emotion regulation have been shown (Bornas, Tortella-Feliu, Balle, & Llabres, 2012). Fractal dimension decreased with increasing rumination and self-blaming. Based on these studies it may be expected that psychological pain will be associated with decreased EEG complexity.

Table 4.1 Sociodemographic and clinical characteristics of the sample ($N = 35$).

Age, Mean years (*SD*)	35.03 (11.84)
Female, *n* (%)	27 (77.1)
Ethnicity *n* (%)	
White	17 (48.6)
African American	3 (8.6)
Hispanic	4 (11.4)
Asian	5 (14.3)
Other or mixed [a]	6 (17.1)
Highest Completed Education *n* (%)	
High school	5 (14.3)
Some college	10 (28.6)
College	12 (34.3)
Graduate/Professional School	8 (22.9)
Marital status *n* (%)	
Single	31 (88.6)
Married/in a relationship	4 (11.4)
Employment status *n* (%)	
Unemployed	14 (40.0)
Occasionally employed	11 (31.4)
Regularly employed	10 (28.6)
Diagnosis *n* (%)	
Major depressive disorder	17 (48.6)
Dysthymic disorder	3 (8.6)
Depression NOS	15 (42.9)
On antidepressants *n* (%)	
yes	16 (45.7)
no	19 (54.3)
Time since D_x, Mean years (*SD*)	6.77 (6.10)

Note. *SD*: standard deviation, NOS: not otherwise specified, D_x: diagnosis.
[a] Other included native Hawaiian, Pacific Islander, native American, and Alaska native.

CHAPTER 4

Methods

Participants

The study sample consisted of right-handed adults ($N = 35$) who had been diagnosed with a depressive disorder (self-reported) at some time in their lives, but who did not necessarily experience a depressive episode at the time of participation. Participants indicated that they were free from cardiovascular abnormalities, as a criterion for inclusion. Of 65 potential participants who passed a phone screening, 38 participants passed a face-to-face screening that included a test for right-handedness (Edinburgh Handedness Inventory laterality score 75) and cognitive impairment (Minicog). Three participants were excluded because of a positive urine drug screen that tested for common drugs of abuse on the day of data collection. Sample characteristics are shown in Table 4.1. Participants were recruited from a psychiatric hospital's outpatient department and psychological services centers in the San Francisco Bay Area of California, and via online advertisement on Craigslist. Participants provided written consent, and the study was approved by the Institutional Review Board at the University of California, San Francisco.

Measurements

Data collection took place in a controlled laboratory environment. Prior to preparation for EEG recording, participants completed the Beck Depression Inventory (BDI) II, the Beck Hopelessness Scale (BHS), and the Beck Scale for Suicide ideation (BSS). These instruments are well validated and widely used (Beck, Steer, & Brown, 1996; Meyer, et al., 2010; Mystakidou, et al., 2008; Nissim, et al., 2010; Yin & Fan, 2000). We found excellent internal consistency (Cicchetti, 1994) for all three measures, with a

Cronbach's α of .88, .88, and .90 for the BDI, BHS, and BSS, respectively. While the participant completed these pen and paper instruments, the investigator was in the same room preparing the EEG electrodes. Following completion of the instruments, the electrodes were put in place and the participant moved to a separate room where resting-state EEG was measured during six consecutive sessions of 5 minutes each. Repeated measures were used to increase reliability of the measurements. Previous research showed little improvement beyond five consecutive measurement sessions (Allen, Urry, Hitt, & Coan, 2004b). Participants were sitting upright in a sound attenuated room (constant 50 dB ambient sound level, mostly from air conditioning) with a low light level. Participants were instructed to keep their eyes closed, sit as still as possible, not focus on anything in particular and let their mind run free, as soon as the door closed that separated the rooms of the participant and the investigator. They were told that closing of the door activated the recording. To let participants get used to the experimental setup, a 2-minute test session preceded the first measurement session. All data were recorded between 9 am and 12 noon. Participants had been instructed to not use coffee or nicotine within 2 hours of their appointment, and to not use alcohol within 12 hours of their appointment. Compliance with these instructions was queried prior to data collection.

The EEG setup (Biosemi ActiveTwo, sample rate 1024 Hz) involved 34 electrodes placed according to the 10/20 system (including left earlobe and mastoid). Individual flat-type electrodes were used to record horizontal and vertical electro-oculograms from the outer canthi of the eyes, and above and below the left eye.

Psychological Pain was assessed with the Psychache Scale (Holden, et al., 2001) and the Orbach & Mikulincer Mental Pain (OMMP) questionnaire (Orbach, et al., 2003b). The Psychache Scale and OMMP were completed between the first and second measurement sessions to be able to assess the effect of completing the questionnaires on frontal EEG asymmetry

(see Chapter 6). After handing them the questionnaires and providing instructions, the participants completed the questionnaires while the investigator waited in the other room and the connecting door was open. The Psychache Scale (Holden, et al., 2001) is a 13-item self-report instrument that taps psychological pain and results in a continuous total score (range 13 – 65). Nine items are scored on a frequency scale ranging from never to always and four items are scored on a symmetrical scale ranging from strongly disagree to strongly agree. The instrument is well validated in diverse populations, including male prison inmates (Mills, et al., 2005), psychology students (DeLisle & Holden, 2009; Troister & Holden, 2010), and men who are homeless (Patterson & Holden, 2012), but evidence for validity in clinical samples is limited (Owoeye, Aina, Omoluabi, & Olumide, 2007). The OMMP questionnaire is a 44-item instrument that taps both current (OMMP_c, at the time the questionnaire was completed) and worst-ever (OMMP_w) psychological pain, resulting in a continuous total score (range 44 – 220) for each. A 5-item response scale ranging between strongly disagree and strongly agree is used for all 44 items. The OMMP was shown to possess a high degree of validity in psychiatric inpatients (Orbach, et al., 2003a; van Heeringen, et al., 2010) and in university students and the general population (Orbach, et al., 2003b). In our sample, excellent internal consistency was found for the Psychache Scale (Cronbach's α .92) and for the OMMP (Cronbach's α of .95 for both the OMMP_c and OMMP_w).

After the last measurement session, the investigator sat down with the participant to briefly talk about how completing the psychological pain measures had affected them. A distress protocol similar to that described by Draucker et al. (2009) was in place, and was triggered by an emotional response beyond what could be expected in a study involving sensitive topics (e.g. uncontrolled crying, incoherent speech, dissociation, agitation). The protocol was also used if a participant's total score on the BSS was 19 or higher, or when they endorsed the most severe option in response to BSS

items 'Wish to die', 'Active suicidal desire', 'Control over action', 'Specificity of planning', or 'Expectancy and anticipation'.

Data Analysis

Issues regarding the processing of raw EEG data into frontal EEG asymmetry were addressed as described by Allen, Coan, and Nazarian (2004a). Raw EEG data were vertex (Cz) referenced offline. A 4^{th} order bandpass filter (0.25 - 256 Hz) was applied, followed by a 2^{nd} order notch filter at 60 Hz and harmonics up to 240 Hz to compensate for main power interference. After automatic artifact rejection, data were divided into nonoverlapping 2 s epochs, which were detrended and windowed using a Hamming window. Fast Fourier transformation (FFT) was used to determine the power spectrum within each epoch. Subsequently, power was determined in standard frequency bands (delta: 0.5 – 4 Hz, theta: 4 – 8 Hz, alpha: 8 – 13 Hz, beta: 13 – 30 Hz, theta: 30 – 100 Hz). Frontal EEG asymmetry (A_{α}) for each epoch was calculated as (F4 – F3)/(F3 + F4), where F3 and F4 represent alpha power at the left (F3) and right (F4) electrodes, respectively. Finally, frontal EEG asymmetry within a measurement session was averaged over all valid epochs. Data processing was done in GNU Octave 3.2.3.

We explored the utility of the fractal dimension with respect to frontal EEG activity and psychological pain. The underlying property of the fractal dimension is called self-affinity or self-similarity, which means that the fractal dimension of a particular signal is the same, irrespective of the timescale at which that signal is observed (Eke, Herman, Kocsis, & Kozak, 2002; Mandelbrot, 1982). We calculated the fractal dimension by means of a box-counting method, which can be visualized by assuming an arbitrary EEG signal plotted against time. For boxes that are progressively smaller in size, it is determined how many boxes are minimally needed to cover the signal. For

a self-similar signal, the box size and the number of boxes that are needed will follow a power law:

$$N(\varepsilon) \propto \varepsilon^{-D}$$

where N equals the number of boxes, ε indicates box size, and D represents the box-counting, or fractal dimension (Shelhamer, 2007). The fractal dimension of a neurophysiological time series falls between 1 and 2 (Eke, et al., 2002; Stam, 2006). Superiority in analyzing signals with a known fractal dimension has been shown for box-counting methods over other popular methods like Katz (Katz, 1988), while being comparable in accuracy to the Higuchi method (Higuchi, 1988) and less computationally intensive (Raghavendra & Narayana Dutt, 2010). The fractal dimension was determined for each epoch that was also included in the standard EEG analysis. Frontal fractal dimension asymmetry for each epoch was calculated similar to frontal α-asymmetry, using fractal dimension values instead of alpha power.

We determined the intraclass correlation coefficient (ICC) for agreement between successive measurement sessions of the individual EEG power components, frontal α-asymmetry, and frontal fractal dimension asymmetry. Excellent agreement was found by conventional standards (Cicchetti, 1994), with ICC values > 0.75 for all repeated measures. It was therefore decided that these variables could be averaged across all six measurement sessions.

When the data were assessed for distribution, it was found that the BSS, OMMP_w, and frontal α-asymmetry were not normally distributed. Further inspection for outliers identified one participant with a OMMP_w z-score of 3.66. As the OMMP_w was normally distributed without this participant, it was decided to exclude the OMMP_w score of this participant.

All statistical tests were computed using PASW Statistics 18.0, and statistical significance was assumed at $p < .05$. Multiple regression was used to determine associations between psychological pain and EEG power components (aim 1), and whether frontal α-asymmetry predicted psychological pain (aim 2).

Results

Sample Characteristics

Sociodemographic and clinical characteristics of the participants are shown in Table 4.1. The average age was 35.0 years (*SD* 11.8), and women made up about three quarters of the sample. The majority of participants were single. The average time since the participants were first diagnosed with depression was 6.8 years (*SD* 6.1). Almost half of the participants had been diagnosed with major depressive disorder, whereas most of the remaining participants endorsed depression not otherwise specified. Almost half of the participants were using antidepressants at the time of the study.

Table 4.2 shows mean scores and correlations between measures of psychological pain, covariates of psychological pain, and EEG asymmetry values. The average level of depression and hopelessness was moderate by conventional standards (Beck & Steer, 1993; Beck, et al., 1996). Cut-off scores for clinical purposes do not exist yet for measures of psychological pain. Current psychological pain in the sample was slightly lower than reported for inpatients admitted for a depressive episode (OMMP_c = 135, van Heeringen, et al., 2010), and lower than reported in women who had recently attempted suicide (OMMP_c = 148, Reisch, et al., 2010). On the other hand, the average Psychache Scale score in our sample was considerably higher than reported in undergraduates (PS = 20.69, Troister & Holden, 2010) and dermatology patients (PS = 28.94, Owoeye, et al., 2007).

The mean frontal α-asymmetry was slightly negative (M = -.01, SD = .07), which indicates relative right (greater right than left) activity. The mean fractal dimension of EEG activity at both midfrontal electrodes was 1.57 (SD = 0.04), resulting in a mean frontal fractal dimension asymmetry of .00 (SD .01).

Table 4.2 Correlations between psychological pain, covariates, and asymmetry measures (N = 35).

		1	2	3	4	5	6	7	8
1.	PS	-	-	-	-	-	-	-	-
2.	OMMP_c	.62***	-	-	-	-	-	-	-
3.	OMMP_w [a]	.19	.43*	-	-	-	-	-	-
4.	BDI	.77***	.67***	.38*	-	-	-	-	-
5.	BHS	.57***	.62***	.32	.64***	-	-	-	-
6.	BSS [b]	.46**	.37*	.31	.59***	.61***	-	-	-
7.	A_{α}	-.05	-.15	-.16	.09	-.32	.05	-	-
8.	A_{fd} [b]	.02	-.34*	-.42*	-.19	-.05	-.16	-.15	-
M		40.60	122.03	179.26	27.23	11.71	4.94	-.01	.00
SD		10.37	27.70	21.81	10.83	5.27	6.05	.07	.01

Note. PS: psychache scale, OMMP_c: Orbach & Mikulincer current mental pain questionnaire, OMMP_w: Orbach & Mikulincer worst-ever mental pain questionnaire, BDI: Beck depression inventory, BHS: Beck hopelessness scale, BSS: Beck Scale for Suicide ideation, A_{α}: frontal α-asymmetry, A_{fd}: frontal fractal dimension asymmetry, M: mean, SD: standard deviation.
[a] n = 34, [b] Spearman instead of Pearson correlations because of nonnormality.
*** $p < .001$, ** $p < .01$, * $p < .05$.

All correlations with covariates of psychological pain were positive, indicating that as expected, psychological pain increased with increasing depression, hopelessness, and suicide ideation (see Table 4.2). Correlations

between worst-ever psychological pain and the Psychache Scale score, hopelessness, and suicide ideation were not significant, but correlations with hopelessness and suicide ideation showed a trend toward statistical significance with $p = .07$ and $p = .08$, respectively. Frontal α-asymmetry did not correlate significantly with any of the self-report measures, including depression, but a statistical trend was observed for the correlation with hopelessness (r_s = -.32, $p = .06$). Significant inverse correlations of medium strength were found between frontal fractal dimension asymmetry and both OMMP measures. Correlations between psychological pain and the left and right fractal dimension were not significant, however, the direction of the associations suggested increased left-sided complexity ($r_s = .12$, $p = .50$ and $r_s = .17$, $p = .33$ for current and worst-ever psychological pain, respectively), whereas decreased right-sided complexity was observed with increasing psychological pain (r_s = -.11, $p = .53$ and r_s = -.03, $p = .87$ for current and worst-ever psychological pain, respectively).

Associations with EEG Power Components

Total EEG power, that is the sum of all EEG frequency components, correlated significantly with worst-ever psychological pain (r = -.32, $p = .07$ and r = -.36, $p = .04$ for left and right total power respectively). Total power correlations with current psychological pain as assessed on the OMMP were negative and nonsignificant (r = -.08, $p = .63$ and r = -.18, $p = .31$ for left and right total power respectively), whereas correlations with the Psychache Scale score were positive and nonsignificant ($r = .11$, $p = .53$ and $r = .19$, $p = .28$ for left and right total power, respectively). Means and standard deviations for all midfrontal EEG power components are shown in Table 4.3. The direction of the association between psychological pain and resting-state frontal brain activity in standard EEG frequency bands was determined through hierarchical multiple regression. To decrease chances of a type I error, the number of statistical tests was minimized by entering all

EEG frequency components simultaneously, after covariates had been entered. Separate regressions were performed for the three measures of psychological pain, and for left and right EEG components.

Table 4.3 Means and standard deviations in ln(μV2) of midfrontal EEG power components ($N = 35$).

	Left (F3)		Right (F4)	
	M	*SD*	*M*	*SD*
total power	17.38	0.49	17.39	0.46
delta	16.52	0.53	16.54	0.52
theta	15.23	0.52	15.23	0.49
alpha	15.61	0.71	15.59	0.68
beta	15.38	0.59	15.42	0.59
gamma	14.71	0.70	14.78	0.86

Regressions for psychological pain as assessed on the Psychache Scale and current psychological pain on the OMMP did not show significant associations between individual EEG components and psychological pain, after controlling for depression, hopelessness, and suicide ideation. For both left and right components, the only association that was consistent in direction across these two measures of psychological pain, was theta power (positive association) and beta power (negative association). For worst-ever psychological pain, after controlling for depression, strong inverse associations were found for left and right frontal delta power (respectively, β = -.71, p = .003 and β = -.52, p = .04). The direction of association for left and right theta power, was the only consistent direction (positive, but not statistically significant) across all measures of psychological pain.

To assess if these associations between psychological pain and delta power were unique to the frontal location, similar analyses were performed for central and parietal electrode pairs (C3 - C4, P3 - P4). For central

electrodes, a significant association was found between worst-ever psychological pain and right delta power (β = -.60, p = .03). For parietal electrodes, a trend toward a significant association was observed for left delta power (β = -.49, p = .10).

Predicting Psychological Pain

A hierarchical regression of the Psychache Scale score on frontal α-asymmetry, after controlling for covariates, resulted in a significant overall model (F = 15.71, df = 3,31, $p < .0005$). However, the contribution of frontal α-asymmetry was not significant (β = -.04, p = .78). A similar result was obtained with frontal fractal dimension in the model, instead of frontal α-asymmetry (F = 17.27, df = 3,31, $p < .0005$, β = .16, p = .17). This indicates that frontal α-asymmetry nor frontal fractal dimension asymmetry predicted significant variance in psychological pain as assessed on the Psychache Scale.

Table 4.4 shows multiple regression results predicting current psychological pain from frontal EEG asymmetry. Covariates of psychological pain were entered into the model first. This showed that suicide ideation did not contribute significant variance to the model, and therefore suicide ideation was removed from further analyses. While the overall model that included frontal α-asymmetry was significant, frontal α-asymmetry itself did not contribute unique variance to the prediction of current psychological pain. With frontal α-asymmetry in the model, the contribution of hopelessness was also nonsignificant, which suggests that hopelessness and frontal α-asymmetry share some of their variance in current psychological pain. Adding frontal fractal dimension asymmetry to the model, instead of frontal α-asymmetry, resulted in a significant overall model (F = 13.34, df = 3,31, $p < .0005$) that predicted 52.1% (adjusted R^2) of the variance in current psychological pain. Frontal fractal dimension asymmetry contributed unique

variance to the prediction of current psychological pain. The variance inflation factor for depression and hopelessness was about 1.70, which suggests that the total variance predicted by the model might be inflated because of collinearity. Frontal fractal dimension asymmetry decreased with increasing psychological pain, indicating greater left than right complexity with increasing psychological pain.

Given the associations found between worst-ever psychological pain and frontal delta power, Table 4.4 also includes regressions based on the unique contributions of left and right delta power. Left frontal delta power did not contribute unique variance to the prediction of current psychological pain (model 4); However, right frontal delta power did (model 5). The overall model including right delta power predicted 53.4% (adjusted R^2) of the variance in current psychological pain ($F = 13.96$, $df = 3,31$, $p < .0005$), after controlling for depression and hopelessness. Less delta power was associated with greater psychological pain.

Table 4.5 shows regressions predicting worst-ever psychological pain. Depression was the only significant covariate of worst-ever psychological pain and was entered into the models first. Model 1 shows the effect of frontal α-asymmetry which, just as with current psychological pain, did not contribute unique variance to the prediction of worst-ever psychological pain. Adding frontal fractal dimension asymmetry instead of frontal α-asymmetry (model 2), resulted in a significant overall model ($F = 6.55$, $df = 2,31$, $p = .004$) that predicted 25.2% (adjusted R^2) of the variance in worst-ever psychological pain. With left frontal delta power in the model, 31.1% of the variance in worst-ever psychological pain (adjusted R^2) was explained, after controlling for depression ($F = 8.45$, $df = 2,31$, $p = .001$). A similar result was found for right frontal delta power ($F = 8.25$, $df = 2,31$, $p = .001$). Both left and right frontal delta power decreased with greater worst-ever psychological pain.

Table 4.4 Hierarchical Multiple Regressions Predicting Current Psychological Pain from EEG Asymmetry and Delta Power after Controlling for Depression and Hopelessness ($N = 35$).[a]

	b	$SE(b)$	β	ΔR^2
Model 1				
BDI	1.17	0.41	.46 **	.44
BHS	1.71	0.85	.33 *	.06
Model 2				
BDI	1.34	0.45	.52 **	.44
BHS	1.23	1.00	.24	.06
A_α	-50.71	57.00	-.13	.01
Model 3				
BDI	1.01	0.40	.39 *	.44
BHS	1.86	0.81	.35 *	.06
A_{fd}	-1057.25	519.11	-.25 *	.06
Model 4				
BDI	1.12	0.41	.44 **	.44
BHS	1.77	0.83	.34 *	.06
F3 delta	-9.77	6.35	-.19	.04
Model 5				
BDI	1.24	0.39	.48 **	.44
BHS	1.70	0.80	.32 *	.06
F4 delta	-14.23	6.32	-.27 *	.07

Note. BDI: Beck depression inventory, BHS: Beck hopelessness scale, A_α: frontal α-asymmetry, A_{fd}: frontal fractal dimension asymmetry, F3 delta: left midfrontal EEG delta power in $\ln(\mu V^2)$, F4 delta: right midfrontal EEG delta power in $\ln(\mu V^2)$.

[a] dependent variable: Orbach & Mikulincer current mental pain (OMMP_c)

** $p < .01$, * $p < .05$.

Table 4.5 Hierarchical Multiple Regressions Predicting Worst-Ever Psychological Pain from EEG Asymmetry and Delta Power, after Controlling for Depression ($N = 34$).[a]

	b	$SE(b)$	β	ΔR^2
Model 1				
BDI	0.82	0.35	.39 *	.14
A_α	-42.59	49.47	-.14	.02
Model 2				
BDI	0.75	0.32	.35 *	.14
A_{fd}	-1405.95	538.46	-.39 *	.16
Model 3				
BDI	0.82	0.31	.38 *	.14
F3 delta	-18.92	5.96	-.46 **	.21
Model 4				
BDI	0.87	0.31	.41 **	.14
F4 delta	-18.96	6.08	-.45 **	.21

Note. BDI: Beck depression inventory, F3 delta: left midfrontal EEG delta power in $\ln(\mu V^2)$, F4 delta: right midfrontal EEG delta power in $\ln(\mu V^2)$, A_α: frontal α-asymmetry, A_{fd}: fractal dimension asymmetry.

[a] dependent variable: Orbach & Mikulincer worst-ever mental pain (OMMP_w)

** $p < .01$, * $p < .05$.

From an exploratory perspective, it was interesting to know if frontal delta power and frontal fractal dimension asymmetry were associated. A strong positive correlation was found for left frontal delta power ($r = .58$, $p < .0005$), but not for right frontal delta power ($r = .26$, $p = .13$).

Discussion

Within the context of the valence model of affect and the motivational direction model of affect, the objective of this study was to determine the direction of association between psychological pain and resting-state frontal brain activity, and to determine whether frontal EEG α-

asymmetry predicted psychological pain. With respect to the latter, no significant association was found between frontal EEG α-asymmetry and psychological pain. The average frontal α-asymmetry value was slightly negative. As alpha power and alpha activity are inversely correlated (Cook, O'Hara, Uijtdehaage, Mandelkern, & Leuchter, 1998; Goldman, Stern, Engel, & Cohen, 2002), negative α-asymmetry indicates relative right activity (greater right than left). This indicates support for the valence model of affect in the context of psychological pain, and suggests withdrawal behavior more than approach behavior with respect to the motivational direction model of affect.

Initial multiple regressions including all power components simultaneously indicated that bilateral frontal delta power decreased with increasing worst-ever psychological pain, but did not change with current psychological pain. When the unique contribution of delta power to current psychological pain was subsequently tested after controlling for depression and hopelessness, right frontal delta power was found to decrease with increasing pain. The strength of this association was medium, whereas medium to strong inverse associations were found between bilateral frontal delta power and worst-ever psychological pain.

The valence model and motivational direction model of affect are based on frontal alpha power, and do not provide a context to interpret the unanticipated findings with respect to delta power. Delta power is typically observed during reduced alertness and sleep (Hlinka, Alexakis, Diukova, Liddle, & Auer, 2010), and is the dominant frequency in slow wave sleep (Knyazev, 2012). Delta power is also observed at medial prefrontal locations when the body is at rest but awake (Alper, et al., 2006; Chen, Feng, Zhao, Yin, & Wang, 2008). The medial prefrontal cortex is part of a resting-state neural network that is known as the default mode network (Broyd, et al., 2009; Raichle, et al., 2001). Activity in this network is attenuated when the brain is task oriented, and the network is more active when the brain is at

rest. Attenuation may be stronger with more demanding tasks (Broyd, et al., 2009). Our finding of decreasing delta power with increasing psychological pain suggests that the default mode network was less activated in participants with higher psychological pain, or in other words, the higher the psychological pain the less participants were at rest. While it remains speculative, participants with high psychological pain may have experienced more autonomic arousal associated with emotion regulation or with rumination about the causes and consequences of their psychological pain (Ottaviani & Shapiro, 2011; Ray, Wilhelm, & Gross, 2008).

We found that, after controlling for depression, the inverse association between frontal delta power and psychological pain was particularly strong for worst-ever psychological pain. Also, worst-ever psychological pain was associated with bilateral reductions in delta power, whereas current psychological pain was associated with right delta power only. These results suggest a state dependent asymmetry in brain activity, which is visible in delta power, more than in alpha power.

While depression accounted for more variance in current psychological pain than frontal delta power, the reverse was true for worst-ever psychological pain. The strong association with worst-ever psychological pain, which the participants most likely experienced well before study participation (days to at least months), suggests lasting neural changes associated with the experience of psychological pain. The cause of these changes remains unclear, however, if they are related to cognitive processes like rumination, appraisal, or emotion regulation, they may be reversible. These findings provide support for including the identifier 'lasting' in the definition of psychological pain (Meerwijk & Weiss, 2011).

Frontal delta power can be a remnant of eye blinking (Hagemann & Naumann, 2001). It is argued that this was not the case in this study. First, participants were instructed to keep their eyes closed. Although this does not preclude blinking entirely, it does make blinking unlikely. Second,

the artifact rejection process would reject most epochs with blinks because the mean and maximum potential within the epoch would be considered outliers, compared to other epochs. Third, worst-ever psychological pain did not only vary with frontal delta power, but also with right central delta power and left parietal delta power.

As an exploratory aim, it was investigated whether frontal fractal dimension asymmetry predicted psychological pain. Contrary to frontal α-asymmetry, it was found that fractal dimension asymmetry did indeed predict psychological pain, after controlling for depression and hopelessness. The direction of the association indicated higher left than right signal complexity. As correlations between individual frontal fractal dimensions and psychological pain were not statistically significant, this study did not find conclusive evidence to draw conclusions about the source of this asymmetry. The direction of the correlations suggest a combination of increasing left-sided complexity and decreasing right-sided complexity with increasing psychological pain. However, the correlations for individual fractal dimensions should be treated cautiously, as they were small and statistically nonsignificant. Fractal dimension asymmetry was found to be a stronger predictor of worst-ever psychological pain than depression. For current psychological pain, depression was a considerably stronger predictor, but fractal dimension asymmetry predicted significant variance in amounts equal to hopelessness. Fractal dimension asymmetry was also found to correlate strongly with frontal delta power, in particular left delta power. If frontal delta power can indeed be seen as an indication of resting-state arousal, fractal dimension asymmetry might be a marker of autonomic arousal.

Psychological pain as assessed on the Psychache scale did not correlate with any of the EEG variables, whether individual power components or asymmetry measures. On the other hand, significant correlations were found for psychological pain assessed on the OMMP. Both the Psychache Scale and OMMP purport to assess psychological pain, and

extensive research supports their validity and reliability (Mills, et al., 2005; Orbach, et al., 2003a; Orbach, et al., 2003b; Patterson & Holden, 2012; Troister & Holden, 2013; van Heeringen, et al., 2010). Differences in instrument instructions may provide an explanation for this disparity. Whereas the OMMP clearly refers to current and worst-ever pain, the Psychache Scale does not specify a time frame. Respondents complete the scale for psychological pain they may have experienced yesterday, last week, or even months ago. This may have allowed for different interpretations among participants, introducing variance that obscured correlations with EEG measures.

As measures of psychological pain have not before been studied in relation to EEG, the results presented here cannot be generalized. The majority of participants were women, and all participants were right handed and had a history of depression. To increase confidence in the findings, the study should be replicated, preferably in a larger sample with equal proportions of men and women. A next step could be to include people who are left handed. As psychological pain is not restricted to people with depression, it would be expedient to enroll participants based on psychological pain level, rather than on a diagnosis of depression. Future EEG studies of psychological pain should include specific measures of autonomic arousal (e.g. skin conductance, heart pre-ejection period), so the hypothesis may be verified that frontal delta power and frontal fractal dimension asymmetry are markers of autonomic arousal associated with psychological pain.

Five

Psychological Pain and Reduced Resting-State Heart Rate Variability in Adults with a History of Depression

submitted for publication

CHAPTER 5

Heart rate variability (HRV), the oscillation in beat-to-beat intervals, is a well-known parameter of autonomic nervous system functioning (Malik, 1996). The autonomic nervous system (ANS) comprises the sympathetic and the parasympathetic or vagal branches. Both branches exert their influence on heart rate simultaneously (Berntson, et al., 1997; Thayer, 2009); however, the sympathetic branch is dominant in states of arousal, whereas the vagal branch is dominant when the body is at rest. Autonomic arousal typically increases heart rate (Critchley, et al., 2000; Sherwood, 2010; Tanida, et al., 2004) and reduces heart rate variability (Porges, 2007; Siepmann, et al., 2008). Gender differences are known to exist in indices of HRV (Agelink, et al., 2001; Antelmi, et al., 2004; Thayer, Smith, Rossy, Sollers, & Friedman, 1998; Young & Leicht, 2011), with lower low-frequency HRV and higher high-frequency HRV in women compared to men. Low-frequency HRV and high-frequency HRV are among the most reliably described parameters of HRV (Porges, 2007). Theories of HRV ascribe autonomic arousal through vagal inhibition a central role in the expression and regulation of emotions (Appelhans & Luecken, 2006), which may be particularly important in people diagnosed with depression. Reduced vagal activity increases heart rate and decreases HRV (Thayer, 2009; Thayer & Brosschot, 2005).

We studied the relationship between HRV and psychological pain, also known as mental pain or emotional pain (Tossani, 2013). Examples of situations that may cause psychological pain include a) the inability to protect oneself or a loved one from injury, disease, or embarrassment, and b) feeling deficient because of a lack of love or affiliation. The needs to love, be loved, to affiliate, and to avoid harm are core psychological needs (Murray, 1938/2008). In his theory of suicide, Shneidman (1998) has noted that frustration of psychological needs may cause unbearable psychological pain. Grief over losing a loved one, for example, represents a frustration of the need to love and be loved, and a frustration of the need to protect someone

who is cared about deeply. Psychological pain is the result of negative appraisal of this inability or deficiency of the self (Meerwijk & Weiss, 2011). Psychological pain endures and takes time to resolve. One does not experience psychological pain for just a few seconds or minutes. Usually, it lasts for hours, days, weeks, or even longer, although the intensity of the pain may vary during that period.

Psychological pain is a prominent symptom in people who experience depression. Several studies have reported high levels of psychological pain in both inpatients and outpatients (Mee, et al., 2011; Olié, et al., 2010; van Heeringen, et al., 2010). Studies in other populations, ranging from university students and people who were homeless to prison inmates, reported strong positive correlations between depressive symptoms and psychological pain (DeLisle & Holden, 2009; Mills, et al., 2005; Orbach, et al., 2003b; Patterson & Holden, 2012).

It has been suggested that psychological pain may be associated with autonomic arousal as the result of reduced vagal activity (Meerwijk, et al., 2013), but the relationship between psychological pain and markers of ANS functioning, like HRV, remains largely unknown. As HRV has been successfully used as biofeedback to alter mood state (Hassett, et al., 2007; Reiner, 2008; Siepmann, et al., 2008), knowledge about the relationship between HRV and psychological pain may be of particular interest for interventions to alleviate psychological pain.

Existing research provides conflicting evidence regarding HRV and depression. A meta-analysis showed that people diagnosed with major depressive disorder (MDD) had significantly lower high-frequency HRV than healthy comparison subjects (Kemp, et al., 2010b). As high-frequency HRV is a marker of vagal influence, these results suggest that depression is associated with increased arousal because of reduced vagal inhibition of the ANS. Kemp et al. (2010b) also reported that tricyclic antidepressants reduced HRV, whereas no differences were found for MDD patients who used selective

serotonin-reuptake inhibitors (SSRI). However, Licht et al. (2010; 2011) found that starting SSRI significantly reduced HRV, whereas stopping reversed the effect. In addition, some large sample studies found no differences in HRV when unmedicated patients were compared with age and gender matched healthy controls (Licht, et al., 2011; Schulz, et al., 2010), while other studies did find lower HRV in unmedicated patients (H.-A. Chang, et al., 2012b; J. S. Chang, et al., 2012; Kemp, et al., 2012). Despite finding no differences based on standard HRV measures, Schulz et al. (2010) found that nonlinear indices of HRV did discriminate unmedicated MDD patients from healthy controls. Overall, these results suggest that reduced HRV is not solely the result of antidepressant use and can at least in part be attributed to depression itself.

The primary aim of this analysis was to examine the relationship between resting-state HRV and psychological pain. Given previous research regarding relationships among psychological pain, depression, and HRV, we expected higher heart rate and lower HRV with increasing psychological pain. A second aim was to compare two self-report measures of psychological pain, the Psychache Scale ([PS], Holden, et al., 2001) and the Orbach & Mikulincer Mental Pain (OMMP) questionnaire (Orbach, et al., 2003b), on their relationships to HRV. Both scales purport to measure psychological pain, but except for an early version of the OMMP (Davie, 2006), the two scales have never been used together. This analysis is part of a larger study on predictors of psychological pain that included measurement of heart rate and electroencephalography (EEG) in people with a history of depression.

Methods

Participants

The study sample consisted of right-handed adults ($N = 35$) who had been diagnosed with a depressive disorder (self-reported), but who did not necessarily experience a depressive episode at the time of participation. Participants indicated that they were free from cardiovascular abnormalities, as a criterion for inclusion. Of 65 potential participants who passed a phone screening, 25 participants dropped out by not showing for a face-to-face screening or data collection. Two more participants were excluded during screening, one because of dread locks, which is problematic for EEG recording, and one because of marijuana use. The remaining 38 participants passed a face-to-face screening that included a test for right-handedness (Edinburgh Handedness Inventory laterality score ≥ 75) and cognitive impairment (Minicog). A urine drug screen on the day of data collection tested for common drugs of abuse. Three participants were excluded because of a positive drug test. Sample characteristics are shown in Table 5.1. Participants were recruited from a psychiatric hospital's outpatient department and psychological service centers in the San Francisco Bay Area of California, and via online advertisement on Craigslist. Participants provided written consent, and the study was approved by the Institutional Review Board at the University of California, San Francisco.

Table 5.1 General characteristics of the participants by gender and antidepressant use.[a]

	Gender		Antidepressants	
	Men ($n = 8$)	Women ($n = 27$)	No ($n = 19$)	Yes ($n = 16$)
Mean age in years (SD)	38.75 (11.91)	33.93 (11.81)	36.79 (11.28)	32.94 (12.50)
Mean years since D_x (SD)	5.88 (5.41)	7.04 (6.36)	7.11 (6.75)	6.38 (5.41)
Diagnosis				
MDD	4	13	8	9
Dysthymic disorder	0	3	2	1
Depression NOS	4	11	9	6
On antidepressants				
yes	1	15		
no	7	12		
Ethnicity				
White	4	13	7	10
African American	2	1	3	0
Hispanic	2	2	2	2
Asian	0	5	4	1
Other or mixed [b]	0	6	3	3
Highest completed education				
High school	2	3	3	2
Some college	3	7	5	5
College	3	9	7	5
Graduate/Professional school	0	8	4	4

	Gender		Antidepressants	
	Men ($n = 8$)	Women ($n = 27$)	No ($n = 19$)	Yes ($n = 16$)
Marital status				
Single	7	24	17	14
Married/in a relationship	1	3	2	2
Employment				
Unemployed	1	13	7	7
Occasionally	5	6	6	5
Regularly	2	8	6	4

Note. D_x: diagnosis, MDD: major depressive disorder, NOS: not otherwise specified.

[a] no significant group differences were observed, except for antidepressant use between men and women ($\chi^2 = 4.61$, $p < .05$) , [b] Other included native Hawaiian, Pacific Islander, native American, and Alaska native.

CHAPTER 5

Measurements

Data collection took place in a controlled laboratory environment. Prior to preparation for measurement of heart rate, participants completed the Beck Depression Inventory II to assess their level of depression. This instrument is well validated and widely used (Beck, et al., 1996; Yin & Fan, 2000). We found excellent internal consistency (Cicchetti, 1994) with a Cronbach's α of .88. Resting-state heart rate was measured during six consecutive sessions of 5 minutes each. Five-minute sessions were used as recommended for short-term HRV measurements by the task force on HRV (Malik, 1996). Relatively short measurements were prompted also because we recorded EEG as part of our larger study, which required the participants to sit as still as possible with their eyes closed. Longer sessions would have increased the likelihood of motion artifacts. Repeated measures were used to increase reliability of the measurements. Previous research involving EEG (Allen, et al., 2004b) showed little improvement beyond five consecutive measurement sessions. Participants were sitting upright in a sound attenuated room (constant 50 dB ambient sound level, mostly from air conditioning) with a low light level. Participants were instructed to not focus on anything in particular and let their mind run free during the measurements. All data were recorded between 9 am and 12 noon. Participants had been instructed to not use coffee or nicotine within 2 hours of their appointment, and to not use alcohol within 12 hours of their appointment. Compliance with these instructions was queried prior to data collection. Two flat-type electrodes were used to measure heart rate (Biosemi ActiveTwo, sampled at 1024 Hz): one on the right collar bone and one on the lower-left abdomen.

Psychological Pain instruments (PS and OMMP) were completed by participants between the first and second recording session to be able to assess the effect on heart rate of completing the questionnaires (data not reported here). The PS (Holden, et al., 2001) is a 13-item self-report

instrument that examines psychological pain and results in a continuous total score. It uses a 5-item frequency response scale ranging from never to always for 9 items, and a 5-item response scale ranging between strongly disagree and strongly agree for the remaining 4 items. The instrument is well validated in diverse populations, including male prison inmates (Mills, et al., 2005), psychology students (DeLisle & Holden, 2009; Troister & Holden, 2010), and men who are homeless (Patterson & Holden, 2012). Evidence for validity in clinical samples is scarce (Owoeye, et al., 2007). The OMMP questionnaire is a 44-item instrument that examines both current (OMMP_c, at the time the questionnaire was completed) and worst-ever (OMMP_w), psychological pain, resulting in a continuous total score for each. A 5-item response scale ranging between strongly disagree and strongly agree is used for all 44 items. The OMMP was shown to possess a high degree of validity in psychiatric inpatients (Orbach, et al., 2003a; van Heeringen, et al., 2010) and in university students and the general population (Orbach, et al., 2003b). Factor analysis has shown the OMMP to comprise nine factors: (1) Irreversibility, (2) Loss of Control, (3) Narcissistic Wounds, (4) Emotional Flooding, (5) Freezing, (6) Self-Estrangement, (7) Confusion, (8) Social Distancing, and (9) Emptiness. A lack of reliable results moved Orbach to no longer use Factor 8 (personal communication, February 17, 2010). For both the PS and OMMP, a higher score reflects greater psychological pain.

Excellent internal consistency (Cicchetti, 1994) was found for the OMMP_c and OMMP_w (both Cronbach's α .95). Detailed analysis of individual factors within the OMMP_c showed good internal consistency for Factors 2, 3, 7 (Cronbach's α .87, .84, and .82, respectively), acceptable internal consistency for Factor 1, 5, 6, 9 (Cronbach's α .79, .73, ,74, and .76 respectively), but only poor internal consistency for Factor 4 and 8 (Cronbach's α .53 and .49, respectively). Similar results were found for the OMMP_w, except that Factors 5, 6, and 9 showed poor internal consistency. These results suggest that, although internal consistency of the overall

OMMP showed a strong measure of the psychological pain construct, some individual items did not contribute very strongly to the subscale factors they purport to measure. Excellent internal consistency was also found for the PS (Cronbach's α .92). The PS is usually considered unidimensional (Holden, et al., 2001; Mills, et al., 2005), although two factors can be distinguished: one factor that comprises the items that are scored on a frequency scale and another factor that comprises the items scored on a scale showing extent of agreement. Analysis of these individual factors showed Cronbach's α to be .91 for Factor 1 (item 1 – 9) and .73 for Factor 2 (item 10 – 13).

Data Analysis

Heart rate data (lower left abdomen minus collar bone electrode, to maximize the signal and reduce signal noise) were visually inspected for artifacts and ectopic heart beats. The longest segment of unaffected data within each measurement session was used for further analysis. Of a total of 210 measurement sessions (6 per participant), 192 sessions could be used in whole (5 minutes). The shortest segment among the remaining sessions was 2 minutes. Data processing was done in GNU Octave 3.2.3. A 2^{nd} order high-pass filter (5 Hz) was applied to compensate for low-frequency drift. Beat-to-beat intervals (RRI) were determined using standard functions available from the Biosig 2.61 package for GNU Octave. The task force on HRV analysis recommended frequency domain analyses for short-term time series (Malik, 1996) and, given the limitations of short-term time series, we focused on low-frequency HRV (0.04 – 0.15 Hz) and high-frequency HRV (0.15 – 0.4 Hz). We used fast Fourier transformation (FFT) to determine these parameters. Prior to FFT, RRI series were detrended and windowed using a Hamming window. It is generally held that high-frequency HRV is under vagal control, and that low-frequency HRV is affected through both the vagal and sympathetic branches (Berntson, et al., 1997; Porges, 2007). The ratio of low-frequency to high-frequency HRV was also calculated. This ratio is often

presented as a measure of relative balance between sympathetic and vagal control, the sympathovagal balance (Montano, et al., 2009), although some evidence suggests that this interpretation may not be accurate (Eckberg, 1997; Porges, 2007).

Promising results have been obtained with nonlinear indices of HRV, which proved to be more sensitive to changes in the complex behavior of HRV than traditional linear measures that work in the time or frequency domain (Kemp, et al., 2010b; Schulz, et al., 2010). Several reviews are available that describe nonlinear measures (Eke, et al., 2002; Shelhamer, 2007; Voss, Schulz, Schroeder, Baumert, & Caminal, 2009b). We explored the utility of the fractal dimension with respect to beat-to-beat intervals. The fractal dimension signifies dynamic complexity (Shelhamer, 2007), capturing nonstationary changes in signal amplitude as well as frequency. The underlying property is called self-affinity or self-similarity (Eke, et al., 2002; Mandelbrot, 1982), which means that the fractal dimension of a particular signal is the same, irrespective of the timescale at which that signal is observed. We calculated the fractal dimension by means of a box-counting method (Shelhamer, 2007), which can be visualized by assuming a physiological signal plotted against time. For boxes that are progressively smaller in size, it is determined how many boxes are minimally needed to cover the signal. For a self-similar signal, the box size and the number of boxes that are needed will follow a power law:

$$N(\varepsilon) \propto \varepsilon^{-D}$$

where N equals the number of boxes, ε indicates box size, and D represents the box-counting, or fractal dimension. The fractal dimension of a physiological time series falls between 1 and 2 (Eke, et al., 2002). Superiority in analyzing signals with a known fractal dimension has been shown for box-counting methods over other popular methods like Katz (Katz, 1988), while

being comparable in accuracy to the Higuchi method (Higuchi, 1988) and less computationally intensive (Raghavendra & Narayana Dutt, 2010).

We determined the intraclass correlation coefficient (ICC) for agreement between successive measurement sessions of average heart rate and HRV. Excellent agreement was found by conventional standards (Cicchetti, 1994), with ICC values of .99, .84, and .97 for heart rate, low-frequency HRV, and high-frequency HRV, respectively. It was therefore decided to average variables for each participant across all six measurement sessions. A natural logarithm was used to transform the frequency domain HRV parameters, to obtain a more normally distributed variable. All statistical analyses were computed using PASW Statistics 18.0, and statistical significance was assumed at $p < .05$.

To assess sample differences based on gender and antidepressant use, *t*-tests were used for continuous data and χ^2 analysis for categorical data. Bivariate correlations and multiple regression procedures were used to determine the relationship between psychological pain and heart rate variables, while controlling for the effect of covariates.

Results

Participant Characteristics

Participants had an average age of 35.03 (*SD* 11.84), and an average of 6.77 years (*SD* 6.10) had passed since they were first diagnosed with depression. The average level of depression at the time of participation was 27.23 (*SD* 10.83), which represents moderate depression by conventional standards (Beck, et al., 1996). The participants' age and time since diagnosis were congruent with previous research that found a median age of onset for mood disorders to be 30 (Kessler, et al., 2005). Table 5.1 shows the general characteristics of the participants by gender and antidepressant use ($N = 35$).

On average, women were more than 4 years younger than men, but this was not statistically significant. The table also shows that 77.1% of the sample were women and that they used antidepressants significantly more often than men. Women are 50% more likely than men to experience a mood disorder in their lifetime (Kessler, et al., 2005), which indicates that men were underrepresented in our sample. Participants in our study predominantly used a variety of SSRIs ($n = 7$) and bupropion ($n = 5$). The remaining four participants used various other types of antidepressant. A trend toward statistically significant differences ($p < .1$) existed in ethnicity between men and women. Women were less often African American or Hispanic (11.1% vs. 50.0% of the men). In women, 18.5% were Asian and 22.2% were mostly of mixed ethnicity or other minority groups. In contrast, none of the men were Asian, of mixed ethnicity, or of other minority groups. Women were more often unemployed (48.1% vs. 12.5%), whereas men were more often occasionally employed (62.5% vs. 22.2%), but these differences were significant at a trend level only.

Psychological Pain

The mean psychological pain scores that were found for the PS and OMMP are shown in Table 5.2. No significant differences were found in mean psychological pain scores with respect to gender or antidepressant use. Table 5.3 shows the correlations between the psychological pain measures. Moderate to strong positive correlations existed between the PS and OMMP_c, and between OMMP_c and OMMP_w.

Table 5.2 Mean and standard deviation of psychological pain and heart rate variables by gender and antidepressant use.[a]

	Gender		Antidepressants		
	Men ($n = 8$)	Women ($n = 27$)	No ($n = 19$)	Yes ($n = 16$)	Total ($N = 35$)
PS	42.63 (9.80)	40.00 (10.63)	39.89 (9.29)	41.44 (11.77)	40.60 (10.37)
OMMP_c	119.25 (27.05)	122.85 (28.35)	119.26 (23.40)	125.31 (32.58)	122.03 (27.70)
OMMP_w	176.88 (22.68)	176.07 (29.65)	175.74 (21.17)	176.88 (35.00)	176.26 (27.90)
HR (1/RRI)	66.52 (12.03)	69.80 (9.91)	68.05 (7.48)	70.24 (13.13)	69.05 (10.34)
LF HRV	5.52 (1.25)	5.30 (0.89)	5.28 (1.16)	5.43 (0.70)	5.35 (0.97)
HF HRV	4.74 (1.04)	5.19 (1.00)	5.06 (1.14)	5.11 (0.88)	5.08 (1.02)
LF/HF	5.19 (6.48)	3.03 (6.44)	4.50 (8.45)	2.37 (2.25)	3.53 (1.02)
FD RRI	1.71 (0.03)	1.71 (0.04)	1.71 (0.04)	1.71 (0.04)	1.71 (0.04)

Note. PS: psychache scale [13 – 65], OMMP_c: Orbach & Mikulincer current mental pain questionnaire [44 – 220], OMMP_w: Orbach & Mikulincer worst-ever mental pain questionnaire [44 – 220], HR: heart rate, RRI: R-R interval, LF HRV: low-frequency heart rate variability in $\ln(ms^2)$, HF HRV: high-frequency heart rate variability in $\ln(ms^2)$, LF/HF: ratio of low-frequency over high-frequency heart rate variability, FD RRI: fractal dimension of beat-to-beat intervals.

[a] no significant differences between men and women or between participants who did and did not use antidepressants.

Table 5.3 Correlations between psychological pain measures and heart rate parameters ($N = 35$).

	1	2	3[a]	4	5	6	7
1. PS	-	-	-	-	-	-	-
2. OMMP_c	.62***	-	-	-	-	-	-
3. OMMP_w [a]	.27	.50**	-	-	-	-	-
4. heart rate (1/RRI)	.24	.13	.15	-	-	-	-
5. LF HRV	.16	-.38*	-.27	-.15	-	-	-
6. HF HRV	-.00	-.03	-.03	-.48**	.30	-	-
7. LF/HF HRV	.01	-.23	-.15	.26	.44**	-.51**	-
8. FD RRI	-.21	-.26	-.04	-.12	.04	.30	.12

Note. PS: psychache scale, OMMP_c: Orbach & Mikulincer current mental pain questionnaire, OMMP_w: Orbach & Mikulincer worst-ever mental pain questionnaire, RRI: R-R interval, LF HRV: low-frequency heart rate variability in $\ln(ms^2)$, HF HRV: high-frequency heart rate variability in $\ln(ms^2)$, LF/HF: ratio of low-frequency over high-frequency heart rate variability, FD RRI: fractal dimension of beat-to-beat intervals.

[a] Spearman instead of Pearson correlations shown because of OMMP_w being positively skewed.

*** $p < .001$, ** $p < .01$, * $p < .05$.

Cut-off scores for clinical purposes do not exist for the measures of psychological pain. Five participants scored above the 75th percentile on the PS (PS > 52), whereas none of the participants scored in this range on the OMMP_c. In contrast, 23 participants scored above the 75th percentile on worst-ever psychological pain (OMMP_w > 176). As both the PS and the OMMP_c purport to assess psychological pain, we compared the two scores after normalization over their respective ranges. A paired samples t-test indicated a significant difference between the two measures ($t(34) = 3.02$, $p < .005$), with participants reporting higher psychological pain on the PS ($M = .53$, $SD = .20$) than on the OMMP_c ($M = .44$, $SD = .16$). This difference

in normalized scores represents a medium to large effect size (r = .48). A Wilcoxon signed-rank test comparing normalized PS scores and worst-ever psychological pain scores showed that scores on the OMMP_w were significantly higher (Mdn = .77) than scores on the PS (Mdn = .52, Z = -4.40, $p < .0005$).

Heart Rate Variability

Table 5.2 shows that differences in average heart rate and HRV between men and women in our sample were not statistically significant. However, they were in the anticipated direction (i.e. higher heart rate and high-frequency HRV, and lower low-frequency HRV and HRV ratio in women). Differences in average heart rate and indices of HRV for participants who did and did not use antidepressants were also nonsignificant (see Table 5.2).

Table 5.3 shows correlations between measures of psychological pain and heart rate variables in the total sample. Only OMMP_c was found to correlate significantly with low-frequency HRV. To illustrate the difference between the two instruments of psychological pain, Figure 5.1 shows low-frequency HRV against psychological pain as assessed by the OMMP_c (panel A) and the PS (panel B). High-frequency HRV and not low-frequency HRV, significantly decreased with increasing heart rate. A trend toward a significant positive correlation existed between low-frequency and high-frequency HRV (p = .09), and between high-frequency HRV and the fractal dimension of beat-to-beat intervals (p = .08).

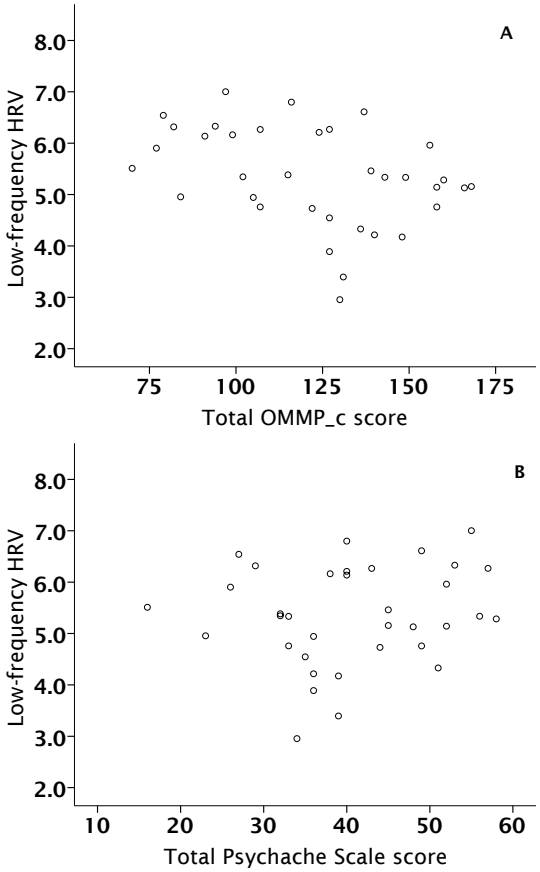


Figure 5.1 Mean low-frequency HRV in ln(ms2) for all participants (N = 35) plotted against psychological pain assessed on the OMMP_c (panel A) and the psychache scale (panel B). HRV: heart rate variability; OMMP_c: Orbach & Mikulincer current mental pain questionnaire.

Low-frequency HRV, high-frequency HRV, and the fractal dimension of beat-to-beat intervals correlated negatively with age (r = -.35, p = .04, r = -.47, p = .005, r = -.41, p = .02, respectively). To further assess their relationships with psychological pain (OMMP_c), while controlling for age and potential interaction effects of antidepressant use (yes/no), we ran simultaneous multiple regression models (see Table 5.4). We did not assess

for potential interaction effects of gender, because the subsample of men was rather small (n = 8). OMMP_c did not predict significant variance in high-frequency HRV. The regression models did not show a main effect of antidepressant use, but a trend toward a significant interaction between antidepressant use and OMMP_c was observed for low-frequency HRV (p = .11) and the beat-to-beat fractal dimension (p = .10). We subsequently ran regression models for the two groups with respect to antidepressant use separately. In the group that did not use antidepressants, OMMP_c explained 41.8% (adjusted R^2) of the total variance in low-frequency HRV (F = 5.75, df = 2,16, p = .01; β = -.47, p = .03), whereas OMMP_c did not explain significant variance in the group that did use antidepressants (β = -.29, p = .29). The predicted low-frequency HRV against psychological pain, while controlling for age and antidepressant use is shown in Figure 5.2. An opposite effect of antidepressant use was found for the beat-to-beat fractal dimension. No significant variance was explained in the group that did not use antidepressants (β = .08, p = .75), whereas OMMP_c explained 49.1% (adjusted R^2) of the total variance in fractal dimension (F = 6.27, df = 2,13, p = .01; β = -.49, p = .03) in the group that did use antidepressants. The fact that the simultaneous regression for beat-to-beat fractal dimension did not show a main effect of OMMP_c (see Table 5.4), whereas a significant contribution of OMMP_c was observed in the group that did use antidepressants, is an example of suppression (Cohen, Cohen, West, & Aiken, 2003), where a suppressor variable (antidepressant use) accounts for variance that would otherwise obscure the relationship between the dependent variable (beat-to-beat fractal dimension) and a predictor (psychological pain). Figure 5.3 shows the predicted beat-to-beat fractal dimension against psychological pain, while controlling for age and antidepressant use. The standardized regression coefficients for OMMP_c in these regression models of low-frequency HRV and beat-to-beat fractal dimension indicate a moderate to large effect size.

Table 5.4 Simultaneous Multiple Regressions Predicting HRV Indices from current psychological pain, while Controlling for Age and Antidepressants ($N = 35$).[a]

	F	R^2	b	$SE(b)$	β
LF HRV	3.63*	23.6%			
age			-0.03	0.01	-.31*
OMMP_c			-0.02	0.01	-.69**
AD			0.15	0.29	.08
AD x OMMP_c			0.02	0.01	.40
HF HRV	2.17	12.1%			
age			-0.04	0.01	-.47**
OMMP_c			-0.00	0.01	-.09
AD			-0.10	0.33	-.05
AD x OMMP_c			0.01	0.01	.10
FD RRI	3.36*	21.7%			
age			-0.00	0.00	-.45**
OMMP_c			0.00	0.00	.10
AD			-0.01	0.01	-.13
AD x OMMP_c			-0.00	0.00	-.42

Note. HRV: heart rate variability in $\ln(ms^2)$, LF: low frequency, HF: high frequency, OMMP_c: Orbach & Mikulincer current mental pain, AD: antidepressant use (yes/no), FD RRI: fractal dimension of beat-to-beat intervals.
[a] age and OMMP_c grand mean centered.
** $p < .01$, * $p < .05$.

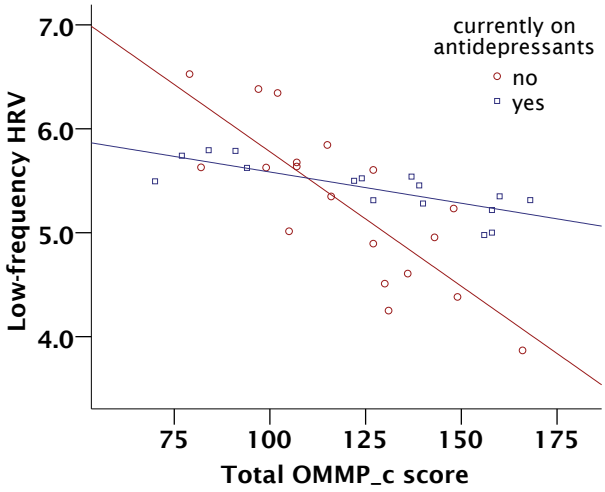


Figure 5.2 Predicted low-frequency HRV in ln(ms2) against psychological pain, controlled for age and antidepressant use. HRV: heart rate variability; OMMP_c: Orbach & Mikulincer current mental pain questionnaire.

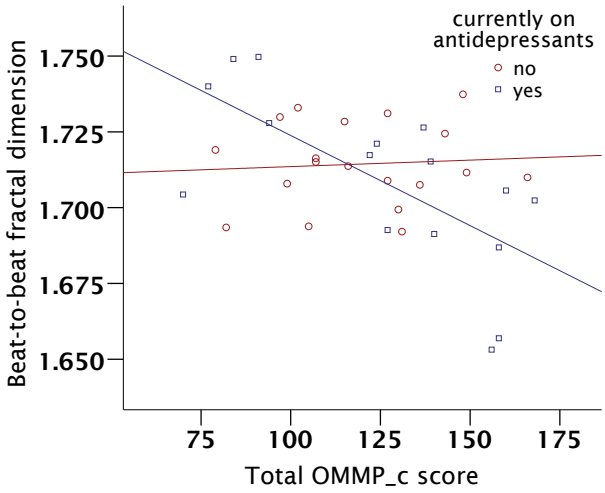


Figure 5.3 Predicted beat-to-beat fractal dimension, controlled for age and antidepressant use. OMMP_c: Orbach & Mikulincer current mental pain questionnaire.

Discussion

We studied the relationship between different measures of psychological pain and HRV in adults with a history of depression. Our hypothesis that psychological pain would be accompanied by decreased HRV was supported in the relationship between OMMP_c and low-frequency HRV and not, as was expected, high-frequency HRV. Low-frequency HRV is believed to reflect a mixture of sympathetic and vagal influences, whereas high-frequency HRV primarily reflects vagal regulation (Berntson, et al., 1997). While researchers have argued that vagal contributions to low frequency fluctuations are significant (Eckberg, 1997), and that the sympathetic and vagal branches of the ANS interact in complex ways to affect low-frequency HRV (Berntson, et al., 1997), the exact role of the sympathetic branch in emotion regulation is still unclear (Appelhans & Luecken, 2006). The trend-level correlation between low-frequency HRV and high-frequency HRV in our data suggests that both branches do interact, but the absence of a significant relationship between psychological pain and high-frequency HRV suggests that vagal influence is not a dominant factor in psychological pain. Taken together, the negative relationship between low-frequency HRV and psychological pain appears to indicate increased sympathetic activity under conditions of greater psychological pain. This effect was most apparent in participants who did not use antidepressants, suggesting potential effects of medication on modulating sympathetic arousal. Previous research has shown that rumination is associated with increased sympathetic activity (Ottaviani & Shapiro, 2011; Ray, et al., 2008). This suggests that people who experience psychological pain, especially those with high psychological pain, may be less adept at reappraising their condition and may ruminate more about their pain and the factors that contribute to it. Interestingly, heart rate was not significantly correlated with psychological pain, nor was it related to either low-frequency HRV or the HRV ratio. Thus

heart rate, typically increased during ANS arousal, does not appear to be a salient marker of psychological pain. It has been suggested that increased arousal during psychological pain may result from reduced vagal activity (Meerwijk, et al., 2013). Our data obtained during resting state do not support that hypothesis.

Studies that reported results for low-frequency HRV in people diagnosed with a depressive disorder are not as abundant as for high-frequency HRV, and it should be noted that comparisons are sometimes complicated because different outcome units are used. Studies that reported HRV in physiological units (Agelink, Boz, Ullrich, & Andrich, 2002; H.-A. Chang, et al., 2012b), while acknowledging a positive correlation between psychological pain and level of depression, appear to support our significant finding of decreased low-frequency HRV with increased psychological pain. Studies that suggest the contrary (Kemp, et al., 2012; Udupa, et al., 2007), do so based on HRV values in normalized units (%) observed in studies that involved methodological differences (shorter measurement session, multiple measurement conditions). Our results are in line with a study of a related phenomenon, pain unpleasantness (Appelhans & Luecken, 2008), that found low-frequency HRV and not high-frequency HRV to predict pain unpleasantness.

We are unaware of studies that reported beat-to-beat fractal dimension based on box counting for people with a history of depression. The fractal dimension in our sample was lower, compared to data in healthy young adults obtained during relatively similar conditions (Guzman-Vargas & Angulo-Brown, 2003). This suggests lower dynamic complexity of beat-to-beat intervals in people with depression compared to healthy people, and is in line with research based on different nonlinear measures (Boettger, et al., 2008; Schulz, et al., 2010), and also with observations in patients with schizophrenia (Bär, et al., 2008). Although, our regression analysis, while controlling for age, did not show a main effect of psychological pain on beat-

to-beat fractal dimension, significantly decreasing complexity of beat-to-beat intervals with increasing psychological pain was apparent in participants who used antidepressants. As antidepressants have been shown to affect sympathetic control of heart rate (Henze, Tiniakov, Samarel, Holmes, & Scrogin, 2013; Licht, Penninx, & de Geus, 2012), our results may suggest that beat-to-beat fractal dimension is an indicator of sympathetic activity. Further study is necessary to explore how antidepressants and different classes of antidepressants affect beat-to-beat complexity.

Despite a strong correlation between the PS score and current psychological pain assessed on the OMMP, the latter was the only psychological pain measure to correlate with participants' physiologic data. This finding may result from structural differences between the OMMP and PS. The first nine items of the PS are rated on a frequency scale (never to always), which do not require psychological pain to be currently present (except when scored always). The remaining four items supposedly assess pain intensity; however, the instructions for the PS do not include a specific time frame. Without specific instructions, participants may have varied in their interpretation of whether to complete the PS for current psychological pain, or for psychological pain that they experienced at some undetermined time in the past. In addition, eight of the 13 items on the PS specifically refer to 'my pain', and do not seem to assess if psychological pain is currently present, but rather the frequency and intensity of psychological pain when it is present. Items on the OMMP, on the other hand, assess different aspects of psychological pain that together give an indication of pain intensity experienced at the moment of completing the questionnaire. Overall, these differences suggest that the OMMP_c is a more accurate measure of current psychological pain intensity than the PS score. In contrast, the PS may better reflect the burden of psychological pain when psychological pain was present at some time in the past. This may be visible in the fact that, when normalized scores are compared, scores on the PS were significantly higher

than those on the OMMP_c, although not quite as high as participants' worst-ever psychological pain (OMMP_w).

Our study was limited by the fact that we relied on self-report regarding participants' diagnosis of a mood disorder. When recruiting participants, we specifically mentioned that they had to have been diagnosed by their health care provider. Also, our sample was not homogeneous with respect to the diagnosis of depression, but rather was chosen to represent an intensity range of depressive symptoms, as this was expected to result in a range of experienced psychological pain. This study was not designed initially to assess differential effects of antidepressant use. Participants were not enrolled to represent specific types of antidepressant, nor did we collect data on prescribed doses. Previous studies have found that different classes of antidepressants modify sympathetic control of heart rate differently (Dawood, Schlaich, Brown, & Lambert, 2009; Licht, et al., 2012). Lastly, we did not assess the overall activity level of the participants. A systematic review reported a significant effect of physical activity on HRV in patients with coronary artery disease (Nolan, Jong, Barry-Bianchi, Tanaka, & Floras, 2008).

The relationship between psychological pain and physiological measures has not been studied previously. We hypothesized that increased psychological pain would be reflected in decreased resting-state HRV and increased heart rate. Neither heart rate nor high-frequency HRV was associated with psychological pain, as assessed by either psychological pain measure. After controlling for age, decreased low-frequency HRV was found to be a salient marker of greater psychological pain. Taken together, these results suggest that a state of arousal occurs during psychological pain, which may result from increased sympathetic activity. In addition, results indicate that the OMMP_c may be a more accurate measure of autonomic arousal associated with current psychological pain than the PS.

Six

Effect of Answering Questions about Psychological Pain on Heart Rate Variability and Frontal EEG Asymmetry

CHAPTER 6

Studies about sensitive topics involve matters such as substance abuse, domestic violence, thoughts of suicide, and end-of-life issues (Rosenbaum & Langhinrichsen-Rohling, 2006; van der Steen, et al., 2012). Tourangeau and Yan (2007) provided three reasons why questions about these topics are considered sensitive: (1) they are considered intrusive and an invasion of privacy, (2) they involve a threat of disclosure, or (3) they elicit an answer that is socially undesirable. Another reason why certain questions may be considered sensitive is that they touch upon deeply felt aspects of the respondent's emotional life, which may cause distress or emotional discomfort. This interpretation fits with Lee and Renzetti's definition of a sensitive topic as "one that potentially poses for those involved a substantial threat ..." (1993, p. 5), the threat being increased emotional discomfort and psychological disintegration. The fundamental feeling that underlies these experiences is psychological pain. Psychological pain, also known as emotional pain or mental pain, has been defined as "a lasting, unsustainable, and unpleasant feeling resulting from negative appraisal of an inability or deficiency of the self" (Meerwijk & Weiss, 2011). Examples of such inabilities and deficiencies are an inability to avoid shame, pain or illness, an inability to protect the self and one's psychological space, or a deficiency in the need to be loved or to achieve things in life (Shneidman, 1998).

Participating in research about sensitive topics is potentially emotionally upsetting, but most individuals who participate in such research report that the benefits of participating outweigh the costs. Newman and Kaloupek (2004) reviewed participant responses in studies on traumatic experiences in a wide variety of populations (e.g. survivors of physical assaults, disasters, child abuse, and partner violence, and trauma-exposed refugees) and reported that, although a small percentage (about 5%) of participants experienced marked upset due to study participation, the majority of these participants did not regret participation. Another review focused on distress in participants in psychiatric research (Jorm, Kelly, &

Morgan, 2007), and reported that a minority of participants (< 10%) experienced emotional distress. They also reported that positive reactions were more common than negative ones, and that participants were more likely to experience emotional distress if they had symptoms of a mental disorder. Among recent studies are a comparison of study-related distress and benefits in participants who completed trauma and sex surveys with those who completed cognitive measures (Yeater, Miller, Rinehart, & Nason, 2012), and a comparison of participants who had and had not experienced child abuse (Decker, Naugle, Carter-Visscher, Bell, & Seifert, 2011). Both studies found that participants who where part of the more discomforting condition (completing trauma and sex surveys, having experienced child abuse) reported more negative emotion due to participating, but were also more likely to report a positive response. Participants in the study by Yeater et al. (2012) also reported that normal life stressors (e.g. having a cavity drilled and filled, having blood drawn, getting a speeding ticket) were experienced as more distressing than having participated in the study. While it is not uncommon for participants in research on sensitive topics to get emotionally upset and report beneficial aspects of study participation at the same time, this cannot be generalized. In a study that included participants who had experienced a traumatic event, 11% of participants responded in ways that could be interpreted as expressing regret about participation (Deprince & Chu, 2008).

None of the studies that were reviewed or recently published included questions that explored psychological pain directly, although many of the study populations can be assumed to have experienced psychological pain. Moreover, all of the reported effects of questions on sensitive topics were based on participant self-report. In the current study, we had an opportunity to examine the effect of questions about psychological pain on three neurophysiological variables: heart rate, heart rate variability (HRV) and frontal electroencephalography (EEG) asymmetry, in people with a

history of depression. A meta-analysis of studies that compared people who had been diagnosed with depression to healthy people (Kemp, et al., 2010b), suggested that people with depression have lower high-frequency resting-state HRV, but no difference in low-frequency HRV. Effects of depression on heart rate are not as clear, with studies reporting no difference (H.-A. Chang, et al., 2012a, 2012b; Licht, et al., 2008), and other studies reporting increased heart rate in people with depression (Agelink, et al., 2002; Koschke, et al., 2009). Another meta-analysis (Thibodeau, et al., 2006) found relative right frontal brain activity, that is, more right than left activity. The valence model of affect , which is based on the distinction between positive and negative emotions (Watson & Tellegen, 1985), holds that relative right frontal activity is linked to negative emotions (Harmon-Jones, 2004; Wager, et al., 2003). High-frequency HRV and low-frequency HRV are among the most reliably described parameters of HRV (Porges, 2007). High-frequency HRV is thought to reflect the influence of the vagal or parasympathetic branch of the autonomic nervous system. Controversy exists about whether low-frequency HRV represents the influence of the sympathetic branch, or a combination of both branches (Appelhans & Luecken, 2006; Montano, et al., 2009), but both branches play a role in emotional arousal. As questions about psychological pain can be considered sensitive in nature and psychological pain is often observed in people with depressive symptoms (Mee, et al., 2011; Olié, et al., 2010; van Heeringen, et al., 2010), we anticipated that participation in the study might be emotionally upsetting for at least some participants. Our aim was to determine whether completing self-report instruments on psychological pain affected resting-state heart rate, HRV, and frontal EEG asymmetry. Assuming that completing these instruments could cause a negative emotional response (i.e. greater experienced psychological pain and/or depressive symptoms) and assuming that this response would linger after completing the instruments, we hypothesized that heart rate would be higher and high-frequency HRV would be lower after the instruments had been

completed, as compared to a baseline measurement. Analogously, we expected frontal EEG activity to shift toward greater relative right activity. Furthermore, we explored whether the effect on HRV and frontal EEG asymmetry would be different for participants who experienced low, medium, or high levels of psychological pain and depression.

Methods

Participants

The study sample consisted of right-handed adults ($N = 35$) who had been diagnosed with a depressive disorder (self-reported) at some time in their lives, but who did not necessarily experience a depressive episode at the time of participation. Participants indicated that they were free from cardiovascular abnormalities, as a criterion for inclusion. Of 65 potential participants who passed a phone screening, 38 participants passed a face-to-face screening that included a test for cognitive impairment (Minicog) right-handedness (Edinburgh Handedness Inventory laterality score ≥ 75). Three participants were excluded because of a positive urine drug screen that tested for common drugs of abuse on the day of data collection. Sample characteristics are shown in Table 6.1. Participants were recruited from a psychiatric hospital's outpatient department and psychological services centers in the San Francisco Bay Area of California, and via online advertisement on Craigslist. Participants provided written consent, and the study was approved by the Institutional Review Board at the University of California, San Francisco.

Table 6.1 Sociodemographic and clinical characteristics of the sample ($N = 35$).

Age, Mean years (*SD*)	35.03 (11.84)
Female, *n* (%)	27 (77.1)
Ethnicity *n* (%)	
White	17 (48.6)
African American	3 (8.6)
Hispanic	4 (11.4)
Asian	5 (14.3)
Other or mixed [a]	6 (17.1)
Highest Completed Education *n* (%)	
High school	5 (14.3)
Some college	10 (28.6)
College	12 (34.3)
Graduate/Professional School	8 (22.9)
Marital status *n* (%)	
Single	31 (88.6)
Married/in a relationship	4 (11.4)
Employment status *n* (%)	
Unemployed	14 (40.0)
Occasionally employed	11 (31.4)
Regularly employed	10 (28.6)
Diagnosis *n* (%)	
Major depressive disorder	17 (48.6)
Dysthymic disorder	3 (8.6)
Depression NOS	15 (42.9)
On antidepressants *n* (%)	
yes	16 (45.7)
no	19 (54.3)
Time since D_x, Mean years (*SD*)	6.77 (6.10)

Note. *SD*: standard deviation, NOS: not otherwise specified, D_x: diagnosis.
[a] Other included native Hawaiian, Pacific Islander, native American, and Alaska native.

Measurements

Data collection took place in a controlled laboratory environment. Prior to preparation for measurement of EEG and heart rate, participants completed the Beck Depression Inventory II to assess their level of depression. This instrument is well validated and widely used (Beck, et al., 1996; Yin & Fan, 2000). We found excellent internal consistency (Cicchetti, 1994) with a Cronbach's α of .88. Participants also completed the Beck Hopelessness Scale and Beck Scale for Suicide Ideation ([BSS], data not reported here). While the participant completed these pen and paper instruments, the investigator was in the same room preparing the EEG and heart rate electrodes. Following completion of the instruments, the electrodes were put in place and the participant moved to a separate room where resting-state heart rate and EEG were measured during six consecutive sessions of 5 minutes each. Participants were sitting upright in a sound attenuated room (constant 50 dB ambient sound level, mostly from air conditioning) with a low light level. Participants were instructed to keep their eyes closed, sit as still as possible, not focus on anything in particular and let their mind run free, as soon as the door closed that separated the rooms of the participant and the investigator. They were told that closing of the door activated the recording. To let participants get used to the experimental setup, a 2-minute test session preceded the first measurement session. To assess the participants' ability to maintain the required resting state without moving or falling asleep, they were asked to give a rating on a 9-point symmetrical scale, ranging from 1 (very easy) to 9 (very difficult), after each session (perceived resting-state scale [PRSS]). All data were recorded between 9 am and 12 noon. Participants had been instructed to not use coffee or nicotine within 2 hours of their appointment, and to not use alcohol within 12 hours of their appointment. Compliance with these instructions was queried prior to data collection.

The EEG setup (Biosemi ActiveTwo, sample rate 1024 Hz) involved 34 electrodes placed according to the 10/20 system (including left earlobe and mastoid). Individual flat-type electrodes were used to record horizontal and vertical electro-oculograms from the outer canthi of the eyes, and above and below the left eye. Two remaining electrodes were used to measure heart beat: one on the right collar bone and one on the lower-left abdomen.

Half way through the data collection phase of the study, it was decided to also record EEG and heart beat *while* participants completed measures on psychological pain (focused attention on psychological pain). As data for many participants had already been collected, EEG and heart beat data during completion of the questionnaires were available for a subsample only ($n = 13$). Approval for this extension was obtained from the Institutional Review Board at the University of California, San Francisco.

Psychological Pain was assessed with the Orbach & Mikulincer Mental Pain (OMMP) questionnaire (Orbach, et al., 2003b) and the Psychache Scale (Holden, et al., 2001). The Psychache Scale and OMMP were completed between the first and second measurement sessions to be able to assess the effect of completing the questionnaires on heart rate, HRV, and frontal EEG asymmetry. After handing them the questionnaires and providing instructions, the participants completed the questionnaires while the investigator waited in the other room and the connecting door was open. The Psychache Scale (Holden, et al., 2001) is a 13-item self-report instrument that taps psychological pain and results in a continuous total score (range 13 – 65). Nine items are scored on a frequency scale ranging from never to always, and four items are scored on a symmetrical scale ranging from strongly disagree to strongly agree. The instrument is well validated in diverse populations, including male prison inmates (Mills, et al., 2005), psychology students (DeLisle & Holden, 2009; Troister & Holden, 2010), and men who are homeless (Patterson & Holden, 2012), but evidence for validity

in clinical samples is limited (Owoeye, et al., 2007). The OMMP questionnaire is a 44-item instrument that taps both current (OMMP_c, at the time the questionnaire was completed) and worst-ever (OMMP_w) psychological pain, resulting in a continuous total score (range 44 – 220) for each. The OMMP was shown to possess a high degree of validity in psychiatric inpatients (Orbach, et al., 2003a; van Heeringen, et al., 2010) and in university students and the general population (Orbach, et al., 2003b). For both instruments, an increase in total score indicates greater psychological pain. In our sample, excellent internal consistency was found for the Psychache Scale (Cronbach's α .92) and for the OMMP (Cronbach's α of .95 for both the OMMP_c and OMMP_w).

After the last measurement session, the investigator sat down with the participant to briefly talk about how completing the psychological pain measures had affected them. If participants indicated they were affected emotionally, they were asked if they thought the emotional discomfort was great enough to potentially affect them the rest of their day and if they would rather not have participated. A distress protocol similar to that described by Draucker et al. (2009) was in place and was triggered by an emotional response beyond what could be expected in a study involving sensitive topics (e.g. uncontrolled crying, incoherent speech, dissociation, agitation). The protocol was also used if a participant's total score on the BSS was 19 or higher, or when they endorsed the most severe option in response to BSS items 'Wish to die', 'Active suicidal desire', 'Control over action', 'Specificity of planning', or 'Expectancy and anticipation'.

Data Analysis

Issues regarding the processing of raw EEG data into frontal EEG asymmetry were addressed as described by Allen, Coan, and Nazarian (2004a). Raw EEG data were vertex (Cz) referenced offline. A 4^{th} order

bandpass filter (0.25 - 256 Hz) was applied, followed by a 2nd order notch filter at 60 Hz and harmonics up to 240 Hz to compensate for main power interference. After automatic artifact rejection, data were divided into nonoverlapping 2 s epochs, which were detrended and windowed using a Hamming window. Fast Fourier transformation (FFT) was used to determine the power spectrum within each epoch. Subsequently, power was determined in standard frequency bands, with alpha power defined as power between 8 – 13 Hz. Frontal EEG α-asymmetry (A_α) for each epoch was calculated as (F4 – F3)/(F3 + F4), where F3 and F4 represent alpha power at the left (F3) and right (F4) midfrontal electrodes, respectively. Finally, frontal EEG asymmetry within a measurement session was averaged over all valid epochs. Data processing was done in GNU Octave 3.2.3.

Heart rate data (lower left abdomen minus collar bone electrode, to maximize the signal and reduce signal noise) were visually inspected for artifacts and ectopic heart beats. The longest segment of unaffected data within each measurement session was used for further analysis. Of a total of 210 measurement sessions (six per participant), 192 sessions could be used in whole (5 minutes). The shortest segment among the remaining sessions was 2 minutes. A 2nd order high-pass filter (5 Hz) was applied to compensate for low-frequency drift. Beat-to-beat intervals (RRI) were determined using standard functions available from the Biosig 2.61 package for GNU Octave. The task force on HRV analysis recommended frequency domain analyses for short-term time series (Malik, 1996) and, given the limitations of short-term time series, we used FFT to determine low-frequency HRV (0.04 – 0.15 Hz) and high-frequency HRV (0.15 – 0.4 Hz) only. Prior to FFT, RRI series were detrended and windowed using a Hamming window. The ratio of low-frequency to high-frequency HRV was also calculated. This ratio is often presented as a measure of relative balance between sympathetic and vagal components of the autonomic nervous system (Montano, et al., 2009),

although questions have been raised regarding this interpretation (Eckberg, 1997; Porges, 2007).

All statistical tests were computed using PASW Statistics 18.0, and statistical significance was assumed at $p < .05$. If appropriate, transformations were used to obtain a more normally distributed variable. To assess sample differences, *t*-tests were used for normally distributed data, and a Wilcoxon signed-rank test was used for nonnormal data. Repeated measures analysis of variance (RMANOVA) and mixed ANOVA were used to determine the effect of answering questions about psychological pain on heart rate, HRV and frontal EEG asymmetry.

Results

Sample Characteristics

Sociodemographic and clinical characteristics of the participants are shown in Table 6.1. Women made up about three quarters of the sample. The majority of participants were single, and almost half of the participants were using antidepressants. The average current psychological pain level on the OMMP was 122.03 (SD = 27.70), whereas the average worst-ever psychological pain was 176.26 (SD = 27.90). A Wilcoxon signed-rank test showed that worst-ever psychological pain was significantly higher than current psychological pain (Z = -5.13, $p < .0005$). To put these scores into perspective, a sample of inpatients admitted for a depressive episode (van Heeringen, et al., 2010) had an average current psychological pain score of 135 (SD = 32.2). The average Psychache Scale score in our sample was 40.60 (SD = 10.37), while the average level of depression was 27.23 (SD = 10.83), which represents moderate depression by conventional standards (Beck, et al., 1996). Because initial data analysis showed that the Psychache Scale

score did not correlate with the neurophysiological variables of interest, the reported results will focus on the OMMP.

Table 6.2 Heart rate variables and EEG variables across measurements ($N = 35$).[a]

	Baseline	1	2	3	4	5	Test [b]
HR	70.62	69.19	68.77	68.68	68.39	68.68	$F = 7.87$ ***, $\varepsilon = 0.67$
LF HRV	5.17	5.31	5.39	5.39	5.40	5.44	$F = 1.17$ (n.s.), $\varepsilon = 0.87$
HF HRV	5.02	5.05	5.06	5.14	5.12	5.12	$F = 0.58$ (n.s.), $\varepsilon = 0.86$
LF/HF	3.66	2.85	3.51	3.60	3.14	4.40	$F = 0.52$ (n.s.), $\varepsilon = 0.51$
F3	15.54	15.65	15.57	15.63	15.64	15.64	$F = 2.84$ *, $\varepsilon = 0.91$
F4	15.50	15.62	15.55	15.61	15.62	15.63	$F = 4.16$ **, $\varepsilon = 0.93$
A_α	-.02	-.01	-.01	-.01	-.01	-.00	$F = 1.15$ (n.s.), $\varepsilon = 1.00$

Note. HR: heart rate in beats/minute, LF HRV: low-frequency heart rate variability in $\ln(ms^2)$, n.s.: not significant, HF HRV: high-frequency heart rate variability in $\ln(ms^2)$, LF/HF: ratio of low-frequency over high-frequency heart rate variability, F3: left midfrontal alpha power in $\ln(\mu V^2)$, F4: right midfrontal alpha power in $\ln(\mu V^2)$, A_α: frontal EEG α-asymmetry.

[a] Psychological pain instruments were completed between baseline and session 1; [b] Within-subjects effect of Time.

*** $p < .0005$, ** $p < .01$, * $p < .05$.

Repeated Measures after Questionnaire Completion

To assess whether heart rate variables and frontal EEG asymmetry after completing the psychological pain questionnaires differed from a baseline measurement, RMANOVAs were conducted with the factor Time representing the six measurements. Table 6.2 shows the results for all variables of interest across the repeated measures. Except for the HRV ratio, all postquestionnaire values were consistently higher or lower than at

baseline. A significant effect of Time was found for heart rate and for both frontal alpha power components (F3 and F4). Individual contrasts showed that heart rate during all postquestionnaire sessions was significantly lower than heart rate at baseline ($p < .005$). With respect to baseline, significantly higher alpha power was found for both components, and for all contrasts except for session 2. As power in the alpha frequency range is inversely correlated with brain activity (Cook, et al., 1998; Goldman, et al., 2002), this signifies lower bilateral activity after the questionnaires were completed.

We continued with a between-subjects ANOVA to assess the effect of Time in groups of participants with low, medium, or high psychological pain. Groups were created based on the participants' OMMP_c score, where $< M - 0.5*SD$ represented the low psychological pain group and $> M +$ 0.5*SD represented the high psychological pain group. Similarly, we created groups with low, medium, or high depression. Because age correlated with the average low-frequency and high-frequency HRV across measurements, and a statistical trend existed for a correlation between age and frontal EEG asymmetry, those analyses were controlled for age. A comparison of psychological pain groups did not show a significant interaction effect of Group x Time for any of the variables of interest. We did find a significant main effect for Group with respect to low-frequency HRV, as participants in the medium and high psychological pain group had significantly lower low-frequency HRV ($p = .02$, $p = .04$, respectively) than participants in the low psychological pain group (see Figure 6.1). No Group x Time interaction effects were found when depression groups where compared, but a significant main effect on heart rate existed for depression group. On average, participants in the high depression group had a significantly higher heart rate ($p = .01$) than participants with a low level of depression (see Figure 6.2).

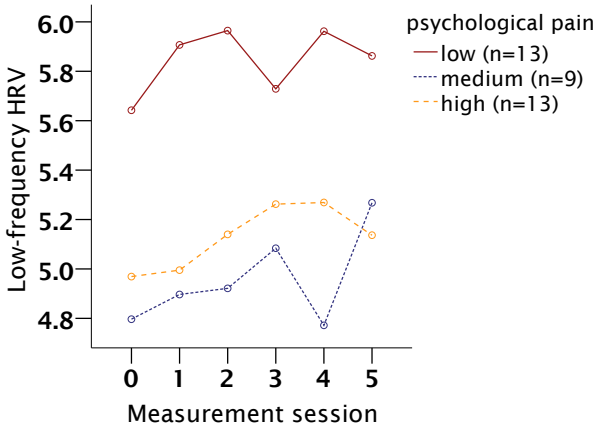


Figure 6.1 Estimated low-frequency HRV in ln(ms2) controlled for age, across measurement sessions and psychological pain groups ($N = 35$). Psychological pain instruments were completed between session 0 (baseline) and session 1. HRV: heart rate variability.

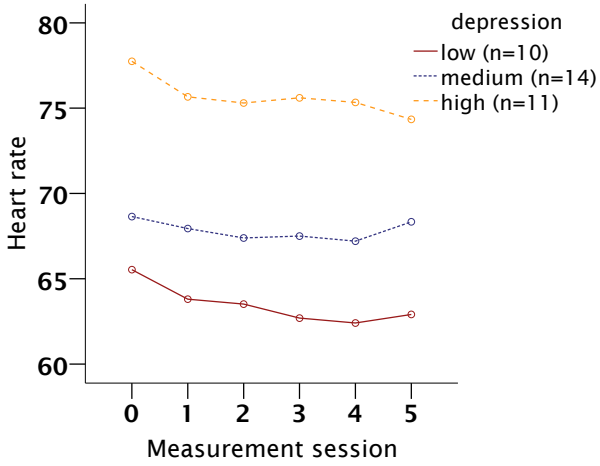


Figure 6.2 Mean heart rate [beats/min], across measurement sessions and depression groups ($N = 35$). Psychological pain instruments were completed between session 0 (baseline) and session 1.

Focused Attention on Psychological Pain

The subsample of participants (n = 13) for whom heart beat and EEG were measured while participants completed the questionnaires on psychological pain did not differ from the remaining participants with respect to sociodemographic variables. However, the subsample scored significantly higher on depression (mean 32.46 vs. 24.14, p = .03), and current psychological pain (mean 136.54 vs. 113.45, p = .02). To determine how the variables of interest were affected during completion of the questionnaires, we conducted RMANOVAs with a three-level Time factor that represented measurements obtained before (baseline), during, and after completion of the questionnaires. The 'after' values constituted averages across the postquestionnaire measurement sessions. The majority of participants in this subsample belonged to the high psychological pain group (9 out of 13), which made Group comparisons unfeasible. Table 6.3 shows the effect of the factor Time for all variables of interest across this analysis. Significant main effects for the factor Time were found for heart rate, low-frequency HRV, the HRV ratio, and both frontal alpha power components. Individual contrasts showed that heart rate during completion of the questionnaires was significantly higher than either before (p = .01) or after completion (p < .0005). Low-frequency HRV during completion of the questionnaires was significantly higher than at baseline (p = .01), but low-frequency HRV after completing the questionnaires was not significantly different from during completion of the questionnaires. The HRV ratio before and after the questionnaires was lower than during completion of the psychological pain questionnaires, but only significantly before the questionnaires (p = .02) were completed. The left and right frontal alpha power during completion of the questionnaires was significantly lower than either before or after completion (p < .0005), indicating more midfrontal brain activity in the alpha range while participants completed the questionnaires.

Table 6.3 Heart rate variables and EEG variables before (baseline), during, and after completion of the psychological pain instruments ($n = 13$).

	Before	During	After [a]	Test [b]	
HR	69.77	71.50	67.11	$F = 17.55$ ***,	$\varepsilon = 1.00$
LF HRV	4.95	5.64	5.23	$F = 4.63$ *,	$\varepsilon = 1.00$
HF HRV	5.04	4.99	5.29	$F = 2.49$ (n.s.),	$\varepsilon = 1.00$
LF/HF	1.79	2.79	2.16	$F = 3.71$ *,	$\varepsilon = 1.00$
F3	15.81	15.06	15.89	$F = 34.90$ ***,	$\varepsilon = 0.63$
F4	15.78	15.05	15.89	$F = 29.05$ ***,	$\varepsilon = 0.61$
A_α	-.01	-.00	.00	$F = 0.26$ (n.s.),	$\varepsilon = 0.75$

Note. HR: heart rate in beats/minute, LF HRV: low-frequency heart rate variability in $\ln(ms^2)$, HF HRV: high-frequency heart rate variability in $\ln(ms^2)$, n.s.: not significant, LF/HF: ratio of low-frequency over high-frequency heart rate variability, F3: left midfrontal alpha power in $\ln(\mu V^2)$, F4: right midfrontal alpha power in $\ln(\mu V^2)$, A_α: frontal EEG α-asymmetry.

[a] Averaged over all postquestionnaire sessions; [b] Within-subjects effect of Time.

*** $p < .0005$, * $p < .05$.

Participant's Responses to Study Participation

On average, the participants reported that maintaining the resting state was relatively easy (see Figure 6.3). The average PRSS score was 3.89, on a symmetrical scale that varied between 1 and 9 (very easy – very difficult). The within-subjects effect of Time showed a trend toward statistical significance ($F = 2.16$, $p = .06$, $\varepsilon = 1.00$), but individual contrasts showed no significant differences in postquestionnaire PRSS scores compared to baseline.

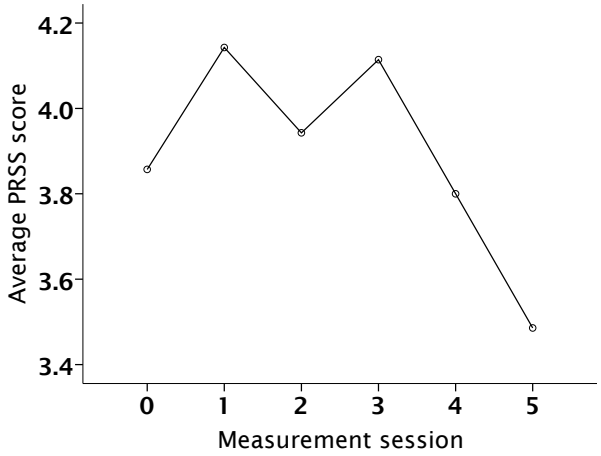


Figure 6.3 Difficulty maintaining the resting state across sessions ($N = 35$). Psychological pain instruments were completed between session 0 (baseline) and session 1. PRSS: Perceived Resting-State Scale.

More than once, participants cried during the face-to-face screening or during the debriefing after the last measurement session; however, their emotional response was never reason to initiate the distress protocol. In other words, their emotional response was never beyond what could be expected. None of the participants who had been upset emotionally by completing the questionnaires on psychological pain, indicated regretting study participation.

Discussion

This study explored the effect of answering questions about psychological pain on resting-state heart rate, HRV, and frontal EEG asymmetry, in people with a history of depression. Psychological pain is a sensitive topic, and it was expected that answering questions about psychological pain might evoke a lasting emotional response that could be visible in these neurophysiological variables.

We hypothesized that heart rate would be higher after completing the psychological pain questionnaires, if completing those questionnaires affected the participants emotionally. For example, Damasio et al. (2000) found heart rate to be increased after recalling an emotionally intense memory (loss of a friend or relative). However, heart rates during all sessions after completing the questionnaires were significantly lower than at baseline, which could suggest that participants experienced little or no lasting emotional effect. While this may have been the case, heart rate during completion of the psychological pain instruments was significantly higher than at baseline, indicating that the focus on psychological pain did increase autonomic nervous system arousal. As the study's design did not include a control group, the extent to which increased heart rate was caused by the sensitive nature of the psychological pain questions remains unknown. Taelman et al. (2011) found that mental load, as compared to a resting condition, increased heart rate. As such, our finding of increased heart rate during completion of the questionnaires could have reflected the mere mental activity of completing the questionnaires. Interestingly, we did not find increased heart rate with increasing levels of psychological pain, whereas we did find increased heart rate with increasing levels of depression, a finding congruent with previous research (Agelink, et al., 2002; Koschke, et al., 2009; Taylor, 2010). Research has also shown that depressive symptoms (specifically, the cognitive and affective components of depression) are associated with reduced heart rate recovery after exposure to stressors (J. L. Gordon, Ditto, & D'Antono, 2012). These findings suggest a larger impact of depression than psychological pain on autonomic arousal and may in part explain why people who have been diagnosed with depression are at higher risk of cardiovascular disease (Lanza, Fox, & Crea, 2006).

Previous research indicates that high-frequency HRV is lower in people with depression, as compared to healthy people, whereas the HRV ratio is higher (Kemp, et al., 2010b). We hypothesized that completing the

psychological pain instruments would have a similar effect in our sample. No significant differences were observed in any of the HRV variables, when postquestionnaire sessions were compared to baseline. However, when examining HRV during actual completion of the questionnaires on psychological pain, low-frequency HRV and the HRV ratio were significantly higher than at baseline. Low-frequency HRV and the HRV ratio remained high after the questionnaires were completed, although not quite as high as during completion of the questionnaires. It is worth noting that the majority of participants in this subsample belonged to the high psychological pain group. Qualitative data showed that the majority of participants in this group also reported that they were a little or more emotionally upset, due to completing the psychological pain instruments. Overall, these results suggest that answering questions about psychological pain affects low-frequency HRV more strongly than high-frequency HRV, especially in people who experience a high level of psychological pain. Increased low-frequency HRV was associated with increased sympathetic nervous system arousal and has been found in people who worry excessively (Hammel, et al., 2011) and in people with chronic stress (Lucini, Di Fede, Parati, & Pagani, 2005), while their high-frequency HRV was decreased. High-frequency HRV was also decreased during a mental load, as compared to a resting condition (Taelman, et al., 2011). If we liken answering questions about psychological pain, which involves ruminating over painful memories, to worrying or stress, our results for increased low-frequency HRV likely point to increased emotional arousal during completion of the questionnaires.

Based on a meta-analysis of resting-state frontal EEG α-asymmetry (Thibodeau, et al., 2006), we hypothesized that completing the psychological pain instruments would shift frontal brain activity in the alpha frequency range toward greater relative right activity. As cortex activity is inversely correlated with alpha power (Cook, et al., 1998; Goldman, et al., 2002), which was the basis of our measure of frontal EEG asymmetry, it was expected that

completing the psychological pain instruments would shift frontal EEG asymmetry toward a lower value compared to baseline. The results did not support our hypothesis and indicated a slight shift toward higher asymmetry values compared to baseline instead. This finding may indicate that completing the measures on psychological pain acted as a form of affect labeling that helped participants manage a negative emotional experience (Lieberman, et al., 2007). The average frontal asymmetry in our sample was slightly above other studies of people with a history of depression (Allen, et al., 2004b; Deldin & Chiu, 2005), who found an average frontal α-asymmetry ranging from -.08 to -.02. Previous research showed that resting frontal asymmetry did not change significantly with changes in severity of depression over time (Allen, et al., 2004b). Hagemann et al. (2002) concluded that resting-state EEG asymmetry appears to be a trait variable, more than an occasion-specific state variable. This may explain the lack of significant differences in frontal EEG asymmetry in our study.

While we did not find significant results for frontal α-asymmetry, midfrontal alpha power was increased after completing the psychological pain questionnaires, especially on the right side. This finding indicates that participants had less cortical activity after focused attention on psychological pain and is congruent with reduced midfrontal alpha activity found previously for individuals with depressive symptoms (Jaworska, Blier, Fusee, & Knott, 2012b; Volf & Passynkova, 2002). Considering previous research, our results could indicate an increase in participants' depressive symptoms or other negative emotion after focusing on their psychological pain. In contrast to the increases in alpha power after completing the questionnaires, alpha power decreased *during* completion of the questionnaires. EEG alpha power is prominent while resting and alert with eyes closed, and alpha power decreases with increasing task demands (International Federation of Societies for Electroencephalography and Clinical Neurophysiology, 1974; Klimesch,

1997). Our finding of reduced alpha power while the questionnaires were completed most likely illustrates this effect.

Some matters of study design should be taken into account when interpreting the results of the study. First, this study was designed to examine the association between psychological pain, HRV, and frontal EEG asymmetry. A repeated measures design was used to increase the reliability of the neurophysiological variables, but simultaneously allowed us to examine the neurophysiological effect of responding to sensitive questions about psychological pain. However, it only allowed examination of those effects for the duration of the measurement sessions ($<$ 30 minutes). A follow-up with participants would be necessary to ascertain that any emotional discomfort was temporary and did not have lasting effects. Participants' responses immediately after the last measurement session were suggestive of temporary discomfort only. Second, for a small subsample of participants, who reported higher depression and higher psychological pain than the sample as a whole, data were collected while they completed the psychological pain instruments. That is, participants were reading the questionnaires, retrieving memories, and contemplating their response. As such the participants were not in a resting state, which violates the assumption that conditions be stationary during resting-state HRV (Malik, 1996). The data were examined for artifacts that the activity may have caused, but obviously we could not control for the altered cognitive and emotional state, as this was precisely what we were interested in measuring. Third, the majority of the participants were women who were not in a relationship, which limits generalizability. Fourth and last, before preparing the participants for EEG and heart rate recording, they completed questionnaires on depression, hopelessness, and suicide ideation. Typically, preparation took 45 minutes until the test session that preceded the baseline recording. During preparation, the investigator and participant talked about everyday topics. While considerable time passed and the preparation activities may have taken the participants' mind off their

emotional state, completing those questionnaires may have primed them and induced a negative mood state at baseline.

Participants in studies about sensitive topics often report benefits of study participation, but may also experience emotional discomfort (Jorm, et al., 2007; Newman & Kaloupek, 2004). We found that answering questions about psychological pain affected heart rate, low-frequency HRV, the HRV ratio, and midfrontal EEG alpha power, especially in people who reported high levels of psychological pain. High-frequency HRV and frontal EEG asymmetry appeared less sensitive and showed no significant differences. Emotional arousal was measurable while participants completed the questionnaires on psychological pain, but except for lingering increased low-frequency HRV and increased alpha power, arousal did not persist during postquestionnaire sessions. Overall, our results suggest that focused attention on psychological pain affects the sympathetic branch of the autonomic nervous system more strongly than the parasympathetic branch.

Seven

Suicidal Desire Moderates Associations between Psychache and Neurophysiology

CHAPTER 7

Previous chapters have addressed psychological pain, frontal electroencephalography (EEG) and heart rate variability (HRV) indices, and described significant associations between psychological pain and low-frequency HRV, and between psychological pain and midfrontal delta power. Some evidence exists, in particular for HRV, that these parameters may be influenced by suicide ideation (Booij, et al., 2006; H.-A. Chang, et al., 2012a, 2012b; Song, et al., 2011). The American Psychiatric Association (2003, p. 9) defined suicide ideation as "thoughts of serving as the agent of one's own death. Suicidal ideation may vary in seriousness depending on the specificity of suicide plans and the degree of suicidal intent". In patients with major depressive disorder and with fully remitted depression, low-frequency HRV and high-frequency HRV were significantly lower in patients with a history of suicide ideation, compared to patients without such history (H.-A. Chang, et al., 2012a, 2012b). A study of North Korean defectors (Song, et al., 2011), with high scores on the Beck depression inventory, found a medium strength negative correlation between high-frequency HRV and suicide ideation, whereas a positive correlation was found for low-frequency HRV (nonsignificant for low-frequency HRV, but significant for normalized low-frequency HRV). Booij et al. (2006) found that in outpatients from a mood clinic, high-frequency HRV significantly reduced after tryptophan depletion in patients with a history of suicide ideation, but not in patients without such history.

Very few studies have investigated resting-state frontal EEG in connection with suicide ideation. Barnhofer et al. (2007) evaluated the effect of meditation, compared to treatment as usual, in people who had been suicidal. Their study did not include a control group, nor did they report correlations between suicide ideation and frontal. Graae et al. (1996) reported on left and right alpha power, the components that determine EEG α-asymmetry, in female adolescents who had attempted suicide. They found that right frontal alpha power was significantly greater than left frontal alpha

power in a control group, suggesting relative left activity. The group who had attempted suicide showed relative right activity (greater right than left), but this difference was not significant. An older EEG review (Struve, 1986) described brief and episodic dysrhythmias in some people with suicidal thoughts and behavior, but the review did not mention resting-state frontal EEG. Overall, studies about EEG α-asymmetry and HRV indicate that suicide ideation may be of importance when assessing the relationship between psychological pain, HRV, and frontal EEG asymmetry, although the effect of suicide ideation may be more prominent for HRV than for frontal α-asymmetry.

Ample evidence supports the notion that psychological pain and suicidal thoughts and behaviors are associated. According to Shneidman's theory of suicide (Shneidman, 1993, 1996), unbearable psychological pain precedes suicidal behavior. Several studies in a variety of populations have found evidence for high levels of psychological pain in people who were suicidal. Measures of psychological pain that were typically used are the Psychache Scale (Holden, et al., 2001), the Orbach & Mikulincer mental pain questionnaire (Orbach, et al., 2003b), and simple numerical scales ranging from 0 to 10, for example (Olié, et al., 2010). Many studies observed a relationship between a history of actual suicide attempts and psychological pain, and found that psychological pain significantly predicted suicide attempter status (zero attempts vs. one or more attempts), after controlling for other important variables, like depression and hopelessness (Patterson & Holden, 2012; Pereira, Kroner, Holden, & Flamenbaum, 2010; Troister & Holden, 2010). Significantly higher psychological pain was found in people who had a history of suicide attempts versus people who had not attempted suicide (Flamenbaum & Holden, 2007; Levi, et al., 2008; Orbach, et al., 2003a). Levi et al. (2008) did not find a significant effect of psychological pain in inpatients with regard to the seriousness of the attempt. Delisle and Holden (2009) found that psychological pain predicted reasons for attempting

suicide, after controlling for depression and hopelessness, and Olié et al. (2010) found that patients who were hospitalized for a depressive episode and who had attempted suicide, reported high current psychological pain more often than inpatients who had not attempted suicide.

Other studies have addressed the relationship between suicide risk and psychological pain, and have generally found that suicide risk increased with psychological pain. Psychological pain predicted self-rated suicide risk after controlling for depression and hopelessness in outpatients with depression (Mee, et al., 2011) and in people from the general population (Soumani, et al., 2011). Psychiatric inpatients who were rated by a therapist to be at risk for suicide, reported significantly higher levels of current psychological pain and worst-ever psychological pain than patients who were not deemed at risk (Pompili, et al., 2008). Of note, Pompili et al. (2008) did not find significant differences in psychological pain when they compared inpatients who had a history of suicide attempts with patients who had not attempted suicide. Furthermore, Soumani et al. (2011) found that tolerance to psychological pain was inversely associated with self-rated risk of suicide.

Still more studies reported on the relationship between the broader concept of suicide ideation and psychological pain. Medium to strong positive correlations were found between a history of suicide ideation and psychological pain in undergraduate students (Holden, et al., 2001; Leenaars & Lester, 2004; Lester, 2000) and in patients admitted for a depressive episode (van Heeringen, et al., 2010). In the only prospective study of psychological pain to date (Troister & Holden, 2012), it was found that in undergraduate students who were thought to be at high risk of suicide at baseline, only change in psychological pain predicted change in suicide ideation over two years, while controlling for depression and hopelessness. In a different study of undergraduates, Troister and Holden (2013) also reported that psychological pain was the stronger predictor of suicide ideation, partially mediating the contributions of depression and hopelessness.

Overall, the literature shows that psychological pain is associated with thoughts about suicide and that psychological pain is higher in people who attempted suicide. This supports the notion that the degree of suicidal intent or suicidal desire may be of import when assessing the relationship between psychological pain and neurophysiological parameters like frontal EEG and HRV. The specific aim addressed in this chapter therefore is to determine whether the associations between resting-state low-frequency HRV and psychological pain, and between right midfrontal delta power and psychological pain are moderated by suicidal desire. In previous chapters that addressed EEG and HRV, Chapters 4 and 5, it has been described that low-frequency HRV and right midfrontal delta power in particular decreased with increasing psychological pain. This chapter also addresses the question of whether HRV predicts psychological pain; one of the research questions for this study.

Methods

Details about the design of the study have been described in Chapters 4 and 5. To address differences in psychological pain between groups based on suicidal desire, two groups were created based on the Beck scale for suicide ideation (BSS) item 4 score. A similar approach was used elsewhere (Booij, et al., 2006; H.-A. Chang, et al., 2012b). BSS item 4 assessed whether participants had a weak or moderate to strong desire to kill themselves in the week before study participation. A subgroup of eleven participants (3 men, 8 women) reported at least a weak desire to kill themselves (BSS item 4 > 0). This group was labeled the "Suicidal Desire" group. An adjusted BSS score was determined that did not include item 4, to maintain independence in BSS score between the two groups. Group differences in psychological pain and clinical covariates were assessed using *t*-tests, Mann-Whitney *U*, and analysis of covariance (ANCOVA). Hierarchical

multiple regression procedures were used to address the question whether an interaction existed for suicidal desire in the prediction of psychological pain.

Results

A description of the sample was provided in Chapters 4 and 5. Table 4.2 shows means, standard deviations, and correlations of all self-report measures, and Table 5.3 shows means, standard deviations, and correlations of psychological pain measures and indices of HRV. Bivariate correlations in these tables indicate that psychological pain as assessed on the Psychache Scale and current psychological pain on the OMMP were significantly associated with depression, hopelessness, and suicide ideation. Worst-ever psychological pain correlated with depression only. Bivariate correlations between measures of psychological pain and low-frequency HRV were significant for current pain on the OMMP only. In addition, a significant bivariate correlation was found between worst-ever psychological pain and right midfrontal delta power (r = -.43, p = .01), whereas bivariate correlations between the Psychache Scale score and right midfrontal delta power and between the OMMP for current psychological pain and right midfrontal delta power were not significant (respectively, r = .22, p = .20 and , r = -.21, p = .24).

Table 7.1 General characteristics of the participants by suicidal desire status.

	Suicidal Desire			
	No ($n = 24$)	Yes ($n = 11$)	Total ($N = 35$)	Test [a]
Mean age in years (SD)	35.42 (11.41)	34.18 (13.27)	34.91 (11.60)	$t = 0.28$
Gender				$\chi^2 = 0.18$
Men	5	3	8	
Women	19	8	17	
Ethnicity				$\chi^2 = 1.32$
White	13	4	17	
African American	2	1	3	
Hispanic	2	2	4	
Asian	3	2	5	
Other or mixed [b]	4	2	6	
Marital status				$\chi^2 = 1.25$
Single	21	10	31	
Married/in a relationship	3	1	4	
Employment status				$\chi^2 = 1.66$
Unemployed	11	3	14	
Occasionally employed	6	5	11	
Regularly employed	7	3	10	
Diagnosis				$\chi^2 = 6.40^*$
Major depressive disorder	15	2	17	
Dysthymic disorder	1	2	3	
Depression NOS	8	7	15	

	Suicidal Desire			
	No ($n = 24$)	Yes ($n = 11$)	Total ($N = 35$)	Test [a]
On antidepressants				$\chi^2 = 0.50$
yes	14	5	19	
no	10	6	16	
Suicide attempts				$\chi^2 = 7.91^*$
Never	21	5	26	
Once	2	2	4	
More than once	1	4	5	
Mean years since D_x (SD)	7.20 (6.56)	5.88 (5.41)	6.88 (6.25)	t = -0.52

Note. NOS: not otherwise specified, D_x: diagnosis.

[a] all χ^2 tests included cells with expected counts less than 5, [b] Other included native Hawaiian, Pacific Islander, native American, and Alaska native.

* $p < .05$.

Clinical Differences With Respect To Suicidal Desire

Participants in the Suicidal Desire group relatively more often indicated a diagnosis of depression NOS and less often major depressive disorder (see Table 7.1). Suicide attempts were more often reported in the Suicidal Desire group than in the group who had no recent suicidal desire (54.5% vs. 12.5%, $p = .02$). Table 7.2 shows means and standard deviations of the self-report instruments scores for both groups. As expected, participants in the Suicidal Desire group, compared to participants who had indicated no recent suicidal desire, scored significantly higher on total suicide ideation (median 11 vs. median 0). The Suicidal Desire group also experienced significantly higher levels of depression, hopelessness and psychological pain as assessed on the PS, but no differences were found for current and worst-ever psychological pain on the OMMP. ANCOVA was used to assess group differences in the PS score, while controlling for depression and hopelessness. This showed no interaction of Group x depression, or Group x hopelessness, and no main effect of hopelessness on the PS score. While controlling for the level of depression, a statistical trend remained for a higher PS score in the Suicidal Desire group ($M = 43.46$, $SD = 6.95$ vs. $M = 39.29$, $SD = 6.74$; $F = 2.58$, $p = .12$, $df = 1,32$). This difference, while taking into account differences in group size (Rosnow, Rosenthal, & Rubin, 2000), represents a small to medium effect size ($r = .25$).

Table 7.2 Means and Standard Deviations of Self-Report Scores by Suicidal Desire Status.

	Suicidal Desire			
	No ($n = 24$)	Yes ($n = 11$)	Test	p
PS	37.42 (9.54)	47.55 (8.87)	t = -2.98	.005
OMMP_c	117.17 (26.76)	132.63 (27.95)	t = -1.57	.13
OMMP_w [a]	176.17 (20.96)	185.72 (23.13)	t = -1.20	.24
BDI	24.42 (10.27)	33.36 (9.79)	t = -2.43	.02
BHS	10.17 (5.02)	15.09 (4.28)	t = -2.81	.008
BSS	1.58 (2.75)	11.18 (4.40)	U = 9.00	< .001

Note. PS: psychache scale, OMMP_c: Orbach & Mikulincer current mental pain questionnaire, OMMP_w: Orbach & Mikulincer worst-ever mental pain questionnaire, BDI: Beck depression inventory, BHS: Beck hopelessness scale, BSS: Beck Scale for Suicide ideation (minus item 4).
[a] $n = 34$.

Predicting Psychological Pain

Previous chapters have indicated that psychological pain as assessed on the Psychache Scale did not correlate with any of the neurophysiological measures. However, differences were found in the Psychache Scale score based on suicidal desire. Table 7.3 shows the results of hierarchical regression models that regressed the Psychache Scale score on low-frequency HRV and right midfrontal delta power, after controlling for covariates and suicidal desire. The overall model that included covariates and low-frequency HRV (model 1) was significant ($F = 19.65$, $df = 3,31$, $p < .0005$, adjusted $R^2 = 62.2\%$) and showed a significant contribution of low-frequency HRV to the total variance in the Psychache Scale score. These regression results show a suppression effect of depression and hopelessness on the relationship between

the Psychache Scale score and low-frequency HRV (Cohen, et al., 2003, pp. 77 - 78). Although the zero-order correlation between the Psychache Scale score and low-frequency HRV was not statistically significant (r = .16, p = .36), a significant positive association became apparent (β = .23, p = .04) when depression and hopelessness were in the regression model suppressing error variance in the Psychache Scale score, and thereby enhancing the relationship between low-frequency HRV and Psychache. Model 2 (see Table 7.3) included suicidal desire and an interaction term for Suicidal Desire x low-frequency HRV. The overall model was significant (F = 13.02, df = 5,29, p < .0005, adjusted R^2 = 63.9%), and showed a trend toward a statistically significant interaction (β = -.22, p = .09) between suicidal desire and low-frequency HRV. Hierarchical regression models for each of the Suicidal Desire groups separately, showed that the overall model was significant for the group *without* suicidal desire only (F = 19.39, df = 3,20, p < .0005, adjusted R^2 = 70.6%). For this group, a significant positive association was found between low-frequency HRV and the Psychache Scale score (β = .39, p = .01). A negative association was found for the Suicidal Desire group, however, this association was not significant (β = -.21, p = .50).

Table 7.3, model 3 shows the results for regression of the Psychache Scale score on covariates and right midfrontal delta power. While the overall model was significant (F = 17.31, df = 3,31, p < .0005, adjusted R^2 = 59.0%), right midfrontal delta power did not contribute unique variance. Model 4 included suicidal desire and an interaction term for Suicidal Desire x right midfrontal delta power. The overall model predicting the Psychache Scale score was significant (F = 15.08, df = 5,29, p < .0005, adjusted R^2 = 67.4%), and showed a significant interaction effect. Individual regression models for the Suicidal Desire groups, showed that the overall model was significant only for the group *without* suicidal desire (F = 17.97, df = 3,20, p < .0005, adjusted R^2 = 68.9%). For this group, a significant positive association was found between right midfrontal delta power and the Psychache Scale score (β

= .33, p = .01), whereas a nonsignificant negative association was found for the Suicidal Desire group (β = -.37, p = .23).

Table 7.3 Hierarchical Multiple Regressions Predicting Psychological Pain as Assessed on the Psychache Scale, after Controlling for Depression, Hopelessness, and Suicidal Desire (N = 35).

	b	$SE(b)$	β	ΔR^2
Model 1				
BDI	0.65	0.13	.67***	.59
BHS	0.35	0.27	.18	.01
LF HRV	2.51	1.15	.23*	.05
Model 2				
BDI	0.62	0.13	.64***	.59
BHS	0.36	0.29	.18	.01
LF HRV [a]	3.09	1.33	.29*	.05
Suicidal Desire	3.41	2.94	.16	.00
SD x LF HRV	-5.91	3.41	-.22†	.03
Model 3				
BDI	0.65	0.14	.67***	.59
BHS	0.25	0.28	.13	.01
F4 delta	3.12	2.22	.16	.02
Model 4				
BDI	0.64	0.12	.67***	.59
BHS	0.17	0.26	.08	.01
F4 delta [a]	5.63	2.20	.28*	.02
Suicidal Desire	3.97	2.44	.18	.02
SD x F4 delta	-14.11	5.03	-.31**	.08

Note. PS: Psychache Scale, BDI: Beck depression inventory, BHS: Beck hopelessness scale, LF HRV: low-frequency heart rate variability in ln(ms^2), SD: recent suicidal desire (yes/no), F4 delta: right midfrontal EEG delta power in ln(μV^2).

[a] grand mean centered.

*** $p < .0005$, ** $p < .01$, * $p < .05$, † $p < .10$.

The regression models for current psychological pain as assessed on the OMMP are shown in Table 7.4. Model 1 shows a significant contribution of low-frequency HRV in the total variance of current psychological pain, after controlling for depression and hopelessness. The overall model was significant ($F = 15.07$, $df = 3{,}31$, $p < .0005$) and predicted 55.4% (adjusted R^2) of the total variance in current psychological pain. Note that the direction of the association between low-frequency HRV and psychological pain in this model was negative, whereas results obtained with the Psychache Scale showed a positive association (see Table 7.3). Adding suicidal desire did not improve the model (model 2), nor was a significant interaction between Suicidal Desire x low-frequency HRV observed. Chapter 4, Table 4 already showed that right midfrontal delta power contributed unique variance to the prediction of current psychological pain, after controlling for covariates. Just like with model 2, adding suicidal desire and the interaction between Suicidal Desire x right midfrontal delta power did not improve the model (see model 4).

Table 7.5 shows the regression models for worst-ever psychological pain as assessed on the OMMP. The overall model that included depression and low-frequency HRV was significant ($F = 3.36$, $df = 2{,}31$, $p = .05$) and predicted 12.5% (adjusted R^2) of the total variance in worst-ever psychological pain. Low-frequency HRV did not contribute unique variance to the prediction of worst-ever psychological pain (model 1), nor was an interaction observed between suicidal desire and low-frequency HRV (model 2). Chapter 4 Table 5 already showed that right midfrontal delta power contributed unique variance to the prediction of worst-ever psychological pain, after controlling for covariates. Like with low-frequency HRV, adding suicidal desire and an interaction term for Suicidal Desire x right midfrontal delta power did not improve the prediction of worst-ever psychological pain (model 4).

Table 7.4 Hierarchical Multiple Regressions Predicting Current Psychological Pain [a], after Controlling for Depression, Hopelessness, and Suicidal Desire ($N = 35$).

	b	$SE(b)$	β	ΔR^2
Model 1				
BDI	1.22	0.38	.48**	.44
BHS	1.38	0.79	.26†	.06
LF HRV	-8.64	3.33	-.30*	.09
Model 2				
BDI	1.15	0.39	.45**	.44
BHS	1.42	0.85	.27	.06
LF HRV [b]	-7.24	3.94	-.25†	.09
Suicidal Desire	7.97	8.71	.14	.00
SD x LF HRV	-14.00	10.10	-.20	.03
Model 3				
BDI	1.24	0.39	.48**	.44
BHS	1.70	0.80	.32*	.06
F4 delta	-14.23	6.32	-.27*	.07
Model 4				
BDI	1.29	0.40	.50**	.44
BHS	1.81	0.84	.35*	.06
F4 delta [b]	-11.18	7.15	-.21	.07
Suicidal Desire	-2.85	7.92	-.05	.00
SD x F4 delta	-15.12	16.36	-.12	.01

Note. BDI: Beck depression inventory, BHS: Beck hopelessness scale, LF HRV: low-frequency heart rate variability in $\ln(ms^2)$, SD: recent suicidal desire (yes/no), F4 delta: right midfrontal EEG delta power in $\ln(\mu V^2)$.

[a] dependent variable: Orbach & Mikulincer current mental pain (OMMP_c), [b] grand mean centered.

** $p < .01$, * $p < .05$, † $p < .10$.

Table 7.5 Hierarchical Multiple Regressions Predicting Worst-Ever Psychological Pain [a], after Controlling for Depression, and Suicidal Desire ($N = 34$).

	b	$SE(b)$	β	ΔR^2
Model 1				
BDI	0.78	0.35	.37*	.14
LF HRV	-4.21	3.63	-.19	.04
Model 2				
BDI	0.64	0.39	.30	.14
LF HRV [b]	-5.39	4.22	-.24	.04
Suicidal Desire	7.49	9.44	.16	.02
SD x LF HRV	0.24	11.26	.00	.00
Model 3				
BDI	0.69	0.41	.33†	.14
BHS	0.52	0.78	.13	.01
F4 delta	-18.97	6.13	-.45**	.21
Model 4				
BDI	0.72	0.33	.34*	.14
F4 delta [b]	-23.68	6.69	-.57**	.21
Suicidal Desire	4.26	7.13	.09	.01
SD x F4 delta	23.25	15.31	.25	.05

Note. BDI: Beck depression inventory, LF HRV: low-frequency heart rate variability in $\ln(ms^2)$, SD: recent suicidal desire (yes/no), F4 delta: right midfrontal EEG delta power in $\ln(\mu V^2)$.

[a] dependent variable: Orbach & Mikulincer worst-ever mental pain (OMMP_w), [b] grand mean centered.

** $p < .01$, † $p < .10$.

As suicidal desire affected the associations with psychological pain as assessed on the Psychache Scale, it was verified whether the associations between psychological pain and other variables of interest in this study (heart rate, high-frequency HRV, frontal EEG α-asymmetry) were also moderated by suicidal desire. However, no interaction effects were observed

between suicidal desire and any of these variables with respect to any of the measures of psychological pain.

Discussion

The specific aim of this chapter was to determine whether the associations between resting-state low-frequency HRV and psychological pain, and between right midfrontal delta power and psychological pain were moderated by recent suicidal desire. Furthermore, the question was addressed of whether HRV predicts psychological pain. The results indicated that low-frequency HRV did indeed predict psychological pain as assessed on the Psychache Scale and OMMP for current psychological pain. Interestingly, opposite directions were found for the associations between these measures of psychological pain and low-frequency HRV, after controlling for covariates. Also, suicidal desire had a moderating effect for associations with psychological pain as assessed on the Psychache Scale. The associations with the OMMP scores remained unaffected.

Based on results presented in previous chapters, it was anticipated that low-frequency HRV and midfrontal delta power would decrease with greater psychological pain as assessed on the Psychache Scale. A tendency in this direction was observed for participants with suicidal desire. These findings did not reach statistical significance, potentially because the number of participants with suicidal desire was small ($n = 11$). Markedly different behavior was observed for participants *without* suicidal desire, whose low-frequency HRV and right midfrontal delta power *increased* with greater psychological pain on the Psychache Scale. Extensive evidence supports the role of EEG delta rhythm in states of motivational urges and salience detection (for a review, see Knyazev, 2012). As psychological pain is thought to result from frustration of psychological needs (Meerwijk & Weiss, 2011; Shneidman, 1998; Thornhill & Wilmsen Thornhill, 1989), increased delta

power may indicate greater perceived salience of frustrated needs, and consequently greater psychological pain, in participants without suicidal desire. The opposite pattern in participants with suicidal desire, which was also observed for current psychological pain on the OMMP in the sample as a whole, could point to a greater level of emotional withdrawal and disengagement (Conner, Duberstein, Conwell, Seidlitz, & Caine, 2001; Horwitz, Hill, & King, 2011; O'Connor, Fraser, Whyte, MacHale, & Masterton, 2009) in people with high psychological pain.

It was found that psychological pain as assessed on the Psychache Scale was higher in participants with suicidal desire. Several studies have found that the Psychache Scale score was higher in people who had attempted suicide (Flamenbaum & Holden, 2007; Patterson & Holden, 2012; Pereira, et al., 2010; Troister & Holden, 2010). Our findings for the Psychache Scale are also congruent with studies that used other scales to assess psychological pain in people who were at risk of suicide (Mee, et al., 2011; Pompili, et al., 2008; Soumani, et al., 2011). The literature with respect to the OMMP and suicidal thoughts and behavior is ambiguous. Orbach et al. (2003a) did not find a difference in OMMP scores when comparing nonsuicidal psychiatric inpatients with healthy controls. However, suicidal inpatients or inpatients who had attempted suicide had significantly higher OMMP scores than healthy controls (Levi, et al., 2008; Orbach, et al., 2003a). Soumani et al. (2011) found that suicidal risk increased with greater psychological pain on the OMMP. Overall, our results suggest that the Psychache Scale may be more sensitive to latent suicidal desire than the OMMP. This difference may reflect the fact that the Psychache Scale was developed within the context of Shneidman's theory of suicide (Holden, et al., 2001), and has important clinical consequences when measures of psychological pain are used for the purpose of suicide prevention.

CHAPTER 7

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General Discussion

This dissertation study explored the relationships between resting-state heart rate variability, frontal EEG asymmetry, and psychological pain in people with a history of depression. Previous research has related psychological pain to *psychological* measures only; predominantly depression, hopelessness, and suicide ideation, which makes this the first to study neurophysiological markers of psychological pain. Chapter 2 and 3 laid down the ground work that defined psychological pain and prompted the study of frontal EEG asymmetry. The literature provided a link between frontal EEG asymmetry and the autonomic nervous system, which is involved in cardiac control determining heart rate and heart rate variability. Frontal EEG asymmetry and heart rate variability have been well studied in people with depression, but not in the context of psychological pain.

Agreement of the variables of interest across repeated measurements in this study was excellent, which allowed using the averages of these variables across measurements for subsequent correlational analysis. This showed strong positive correlations between psychological pain as assessed on the Psychache Scale and the OMMP for current psychological pain, depression, and hopelessness. Positive correlations of medium strength were found between worst-ever psychological pain, depression, and hopelessness. Positive medium strength correlations were also found between all measures of psychological pain and suicide ideation. The following will address the aims and related hypotheses of the study.

> **Aim 1**: to determine whether resting-state frontal EEG α-asymmetry predicts psychological pain, after controlling for depression, hopelessness, and suicide ideation.
>
> Hypothesis: greater psychological pain will be associated with relative right (greater right than left) frontal alpha activity.

Chapter 4 showed nonsignificant inverse correlations between frontal α-asymmetry and measures of psychological pain, which indicates that frontal α-asymmetry did not predict psychological pain and cannot be regarded as a marker of psychological pain. The direction of the association between frontal α-asymmetry and measures of psychological pain was consistent, showing greater relative right alpha activity with greater psychological pain. However, these associations were not statistically significant, indicating that the results were not sufficiently persuasive to accept the hypothesis. The average frontal α-asymmetry in the sample was negative, which is in line with research on people with depression (Allen, et al., 2004b; Deldin & Chiu, 2005). As depression and psychological pain were positively correlated, negative frontal α-asymmetry underscores the fact that psychological pain is an unpleasant feeling, and puts psychological pain left of the vertical axis in the circumplex model of affect (see Figure 1.1).

> **Aim 2**: to determine the direction of associations between psychological pain and resting-state frontal activity in standard EEG frequency bands, while controlling for selected covariates.
>
> Hypothesis: greater psychological pain will be associated with less right frontal activity in frequency ranges other than alpha.

Research aim 2 was also addressed in Chapter 4. In regression models that included all EEG frequency components simultaneously, the only association that was consistent in direction across all measures of psychological pain was with frontal *theta* power (positive association, but not statistically significant). No significant associations were found between any EEG frequency component and psychological pain as assessed on the Psychache Scale. However, a significant inverse association of medium

strength was found for right frontal delta power and current psychological pain as assessed on the OMMP. Medium to strong inverse associations were found between left and right frontal delta power and worst-ever psychological pain. These findings for delta power corroborate the hypothesis of less right activity with greater psychological pain, and suggest an asymmetry in resting-state delta power for current psychological pain.

Delta power is associated with the brain's default mode network (Alper, et al., 2006; Chen, et al., 2008). This is a resting-state network that is activated when the body and the brain are at rest (Broyd, et al., 2009; Raichle, et al., 2001). Activation of this network results in more delta power. Our finding of reduced delta power during greater psychological pain suggests less activation of the default mode network and that participants with greater psychological pain were less at rest. The latter is congruent with increased arousal that was reported in Chapter 5.

As the participants were first diagnosed with depression five years (median) before this study, it is likely that they experienced their worst-ever psychological pain well before the study. Virtually all participants rated their worst-ever psychological pain higher than the psychological pain they experienced at the time when they participated. The fact that a significant association was found between frontal delta power and worst-ever psychological pain suggests lasting changes in the default mode network. The cross-sectional nature of the analysis does not allow conclusions about whether these changes were caused by the participants' psychological pain, nor can it be concluded that these changes are permanent. These findings implicate left frontal delta power as a trait marker of psychological pain, because left frontal delta power was not associated with current psychological pain. As right frontal delta power was associated with both current and worst-ever psychological pain it may prove to be a state marker of psychological pain.

The findings for total EEG power measured at the right midfrontal location suggested decreasing activity with increasing current and worst-ever psychological pain as assessed on the OMMP. This supports the review presented in Chapter 3, which found that psychological pain was associated with decreased activity in the right ventromedial prefrontal cortex. As the spatial accuracy of EEG, as compared to for example functional magnetic resonance imaging, is limited (Apkarian, et al., 2005), activity at the midfrontal electrodes can be taken as an approximation of medial prefrontal cortex activity only.

> **Aim 3**: to determine whether heart rate variability predicts psychological pain, after controlling for depression, hopelessness, and suicide ideation.
>
> Hypothesis: greater psychological pain will be associated with less heart rate variability.
>
> Hypothesis: the postulated state of arousal evoked by psychological pain results from decreased parasympathetic activity.

Although much of the results with respect to heart rate variability were discussed in Chapter 5, this specific aim was addressed directly in Chapter 7. It was found that low-frequency heart rate variability did predict psychological pain as assessed on the Psychache Scale and on the OMMP for current pain. Findings for the latter corroborated the associated hypothesis of an inverse association between psychological pain and low-frequency heart rate variability. Associations with the Psychache Scale were moderated by suicidal desire, and will be discussed in the Additional Findings section.

Lower heart rate variability indicates greater arousal (Porges, 2007; Siepmann, et al., 2008), which suggests greater arousal with greater psychological pain. As high-frequency heart rate variability is a marker of parasympathetic nervous system activity (Berntson, et al., 1997; Porges, 2007), and no association was found between high-frequency heart rate variability and psychological pain, these results do not support the hypothesis that the state of arousal evoked by psychological pain resulted from decreased parasympathetic activity. Instead, arousal associated with psychological pain appears to result from increased sympathetic nervous system activity, because low-frequency heart rate variability is thought to be under sympathetic control. The findings suggest that resting-state low-frequency heart rate variability may be a marker of psychological pain.

Previous research has shown that rumination is associated with increased sympathetic nervous system activity (Ottaviani & Shapiro, 2011; Ray, et al., 2008). It is speculated that people who experience psychological pain, especially those with high psychological pain, may be less adept at reappraising their condition and may ruminate more about their pain. Rumination would then lead to increased arousal, as reflected in decreased low-frequency heart rate variability and, as was discussed before, decreased frontal EEG delta power.

> **Aim 4**: to determine whether resting-state frontal EEG α-asymmetry and heart rate variability are decreased after completion of questionnaires on psychological pain, when compared to a baseline recording.

Repeated measures analysis (see Chapter 6) showed that neither frontal EEG α-asymmetry nor heart rate variability were significantly different from baseline after completion of the psychological pain questionnaires. Halfway through the data collection phase of the study, it was

decided to also collect data *while* the participants completed the psychological pain questionnaires (focused attention on psychological pain). Comparison of focused attention on psychological pain with the baseline resting state showed that completing the questions about psychological pain significantly increased heart rate and low-frequency heart rate variability, especially in people who reported high levels of psychological pain. Again, significant differences were not found for high-frequency heart rate variability or for frontal EEG asymmetry. These results suggest that focused attention on psychological pain may affect the sympathetic branch of the autonomic nervous system more strongly than the parasympathetic branch. The findings of this analysis are limited by the fact that collecting EEG while participants completed questionnaires on psychological pain, violates the assumption that conditions be stationary during resting-state heart rate measurements (Malik, 1996).

Although significant differences across repeated measures were not found for frontal EEG asymmetry, midfrontal alpha power was consistently higher than baseline during measurements obtained after the psychological pain questionnaires had been completed. As some evidence exists for increased frontal alpha power in people with depression (Jaworska, et al., 2012b; Volf & Passynkova, 2002), our finding could suggest an increase in perceived depression or other negative emotion after completion of the questionnaires. However, changes in frontal EEG asymmetry across repeated measures, while not statistically significant, do not support that interpretation. Overall, completing questionnaires on a sensitive topic like psychological pain does not appear to have adverse effects on frontal EEG α-asymmetry or heart rate variability.

> **Secondary aim**: to compare traditional analytic approaches of frontal EEG α-asymmetry and heart rate variability with a measure based on nonlinear dynamical systems theory.

The traditional approach to analysis of neurophysiological signals is often based on determination of power spectral density, the variance of a signal across distinct frequency ranges, which requires transformation of the data to the frequency domain. EEG delta power and low-frequency heart rate variability are examples of that approach. Fractal dimension is a nonlinear measure that combines the variance and frequency aspect into a single measure that can be calculated from a time series directly. The fractal dimension signifies dynamic complexity (Shelhamer, 2007), capturing nonstationary changes in signal amplitude as well as frequency. The fractal dimension is but one nonlinear measure from a range of measures that are available (Eke, et al., 2002; Hegger, Kantz, & Schreiber, 1999; Voss, Schulz, Schroeder, Baumert, & Caminal, 2009a). It was chosen because of its applicability to analysis of heart rate and EEG (Stam, 2005; Voss, et al., 2009a), and its applicability to a wide variety of natural phenomena (Mandelbrot, 1982).

Regular statistical analyses (e.g. means, regressions etc.) were applied to assess the fractal dimension of heart beat and frontal EEG. Chapter 4 evaluated an EEG asymmetry measure in which left and right frontal fractal dimension replaced left and right frontal power in the alpha frequency range. It was found that EEG asymmetry based on fractal dimensions decreased with increasing current and worst-ever psychological pain as assessed on the OMMP. In a regression model, fractal dimension asymmetry also predicted psychological pain, that is asymmetry contributed unique variance to psychological pain, above and beyond the variance contributed by covariates. Fractal dimension asymmetry was a stronger

predictor of worst-ever psychological pain than depression, and contributed unique variance to current psychological pain in amounts equal to hopelessness.

Contrary to frontal α-asymmetry, it was found that fractal dimension asymmetry did indeed predict psychological pain, after controlling for depression and hopelessness. The direction of the association indicated greater left than right signal complexity, with increasing psychological pain. Research has indicated that greater complexity, that is a higher fractal dimension, is associated with a healthier system (Delignieres & Marmelat, 2012; Voss, et al., 2009a). This may suggest that psychological pain affects the right frontal cortex more adversely than the left frontal cortex, and that perhaps interventions to alleviate psychological pain should target the right frontal cortex in particular. The results also suggest that fractal dimension asymmetry is more sensitive to neural changes related to psychological pain than frontal α-asymmetry. As fractal dimension asymmetry was also found to correlate strongly with left frontal delta power, which is associated with resting-state arousal and worst-ever psychological pain, this indicates that fractal dimension asymmetry may be a marker of lasting neural changes associated with a history of psychological pain.

We found no significant correlation between the fractal dimension of beat-to-beat intervals and any of the psychological pain measures, which was taken as an indication that beat-to-beat fractal dimension does not predict psychological pain. The next section suggests that it may be necessary to control for antidepressants, as the association between beat-to-beat fractal dimension and psychological pain depended on antidepressant use.

CHAPTER 8

Additional Findings

Chapter 5 addressed the question of whether antidepressant use affected the relationship between psychological pain and heart rate variability. Previous research has found that heart rate variability may be affected by antidepressants. This study found that low-frequency heart rate variability decreased with increasing current psychological pain, as was described before, but statistically significant only in participants who did *not* use antidepressants. This suggests that antidepressants suppress sympathetic nervous system arousal associated with psychological pain. On the other hand, the beat-to-beat fractal dimension decreased with increasing psychological pain in participants who *did* use antidepressants. While suppression of arousal may seem desirable, reduced complexity of beat-to-beat intervals indicates a less healthy cardiac control system (Delignieres & Marmelat, 2012; Voss, et al., 2009a) that may be related to antidepressant use. The relationship between high-frequency heart rate variability and psychological pain did not depend on antidepressant use.

With exception of Chapter 7, all data-based chapters reported no significant associations between neurophysiological variables and psychological pain as assessed on the Psychache Scale, whereas significant associations existed for psychological pain as assessed on the OMMP. This was observed, despite the fact that both measures purport to assess psychological pain and a strong positive correlation existed between the Psychache Scale and the OMMP for current psychological pain. These findings would suggest that the OMMP is a more accurate measure of neurophysiology associated with current psychological pain than the Psychache Scale. As the Psychache Scale's instructions do not include a reference time frame (e.g. current pain, pain during the past two weeks), this may have caused different interpretations among participants and introduced measurement error that obscured correlations with EEG measures and heart rate variability.

Interestingly, psychological pain as assessed on the Psychache Scale was significantly higher in participants with recent suicidal desire compared to participants for whom suicidal thoughts had been longer ago or not at all present. The OMMP scores did not differ between these two groups. This may reflect the roots of the Psychache Scale, which was developed in the context of Shneidman's theory of suicide (Holden, et al., 2001), whereas the OMMP was based on any aversive life event or personal issue that evoked psychological pain (Orbach, et al., 2003b).

Recent suicidal desire also moderated the association between low-frequency heart rate variability and the Psychache Scale score, and between right midfrontal delta power and the Psychache Scale score. Although not significant for participants with recent suicidal desire, the direction of those associations was congruent with other results found in this study (decreased low-frequency heart rate variability and decreased right midfrontal delta power with greater psychological pain on the OMMP). Surprisingly, a statistically significant association in opposite direction (positive instead of negative) was observed between those variables for participants *without* suicidal desire, who experienced less psychological pain than participants with recent suicidal desire. These findings may indicate a greater perceived salience of frustrated needs, and consequently greater psychological pain, in participants without suicidal desire. A similar moderating effect of suicidal desire was not found for associations with current psychological pain as assessed on the OMMP. This would suggest that the Psychache Scale and the OMMP are sensitive to different underlying processes in people with less severe psychological pain. It is hypothesized that the Psychache Scale may be more sensitive to the valence aspect of psychological pain, whereas the OMMP may be more sensitive to the arousal aspect of psychological pain. Notably, EEG delta rhythm is generated in brain areas that are thought to be part of the brain reward system (Knyazev, 2012); the same neural system that is also thought to underlie the valence dimension of the circumplex

model of affect (Posner, et al., 2005). As the Psychache Scale appears to be more sensitive to latent suicidal desire than the OMMP, the Psychache Scale may be preferable in the context of suicide prevention.

The cross-sectional nature of the analysis does not provide direct information about the position of psychological pain along the arousal axis of the circumplex model of affect (see Figure 1.1). Based on the definition and etiology of psychological pain (see Chapter 2), psychological pain might be placed close to the affect labels Frustrated and Distressed. This may be particularly appropriate for people without suicidal desire, as valence and arousal in people with a suicidal desire may depend on their attitude toward suicide. This interpretation for people without suicidal desire is supported by the study's findings of increased resting-state arousal and greater salience of frustrated needs, and puts psychological pain well above the labels Sad and Depressed. This provides additional support for psychological pain as a symptom that is distinct from depressed mood in clinical depression.

Limitations

This dissertation study was not designed to allow generalization of the results to populations other than the sample that was enrolled, but given a similar experimental setup and sample of participants, results may be expected to be similar to the findings of this study. Some limitations of generalizability to other populations exist by the study's design: right-handed adults with a history of depression were eligible only. Also, we did not assess the participants for physical activity or smoking status, both of which may have had an impact, particularly on heart rate variability (Dinas, Koutedakis, & Flouris, 2012; Nolan, et al., 2008). Although data collection included repeated measures of EEG and heart rate to increase reliability of the measurements, with exception of the chapter about the effect of completing questionnaires on psychological pain, the analytic methods were essentially

cross-sectional. These methods, do not allow conclusions about the causal relationship between psychological pain and neurophysiological data that were collected. Other limitations resulted from the sampling strategy, which involved self-nomination. The majority of the participants were young adult women who were not in a relationship. Also, demand characteristics (Orne, 1962), which involves study participants forming an opinion about what the investigator expects to find, may have affected the participants' responses on the self-report instruments. Within the boundaries set by these limitations, this dissertation study contributed compelling new knowledge to our understanding of the neurophysiology associated with psychological pain.

Implications for Future Research

The results of this study were based on a small and predominantly female sample. Also, this was the first study to observe the relationship between neurophysiological variables and psychological pain. Therefore, replication of the findings in other studies is necessary to increase confidence in this study's findings. Use of a control group that does not experience psychological pain at the time of data collection will further enhance interpretation of the data. Future research should control antidepressant use more tightly, as some results depended on whether or not participants used antidepressants at the time of the study. Evidence is emerging that different kinds of antidepressants may affect heart rate variability differently. It is also preferable to ask participants what time reference is used to complete the OMMP for worst-ever psychological pain. Knowledge about the time that has elapsed since the participants experienced their worst-ever pain may yield additional insight into the relationship between worst-ever psychological pain and frontal EEG delta power. Given the moderating effect of suicidal desire on associations between psychological pain as assessed on the Psychache Scale and neurophysiological parameters, it is important to verify this unexpected finding, especially as a similar effect was not found for

associations with the OMMP. Following replication of this study's findings, it should be investigated whether the results generalize to other populations (e.g. people who are left handed). As psychological pain is ubiquitous and not restricted to people with depression or other mental illness, it should be investigated whether the findings of this study generalize to the general population.

Several findings also warrant further investigation. First, psychological pain was linked to low-frequency heart rate variability, which was suggested to be associated with sympathetic nervous system activity. Future studies of psychological pain should include specific measures of sympathetic nervous system arousal (e.g. skin conductance, heart pre-ejection period) to verify this association between psychological pain and the sympathetic nervous system. Also, as low heart rate variability has been associated with an increased risk of cardiovascular disease, it may be prudent to monitor people who experience high psychological pain more closely for adverse cardiac events. Second, a strong correlation was observed between midfrontal delta power and worst-ever psychological pain, which suggested lasting neural changes associated with psychological pain. It should be studied whether these changes persist over time. Third, it is recommended that a reference time frame (e.g. psychological pain during the past week) be added to the Psychache Scale's instructions, to avoid differences in interpretation by respondents. Fourth and last, it should be studied if low-frequency heart rate variability and frontal delta power are amenable to experimental manipulation and whether this affects the experience of psychological pain. This is an important step toward an intervention to alleviate psychological pain.

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Samenvatting (Summary in Dutch)

De meeste mensen hebben ervaring met pijn. We leren al jong dat het aanraken van een heet fornuis of vallen met de fiets onplezierig is. Door deze ervaringen gaan we pijn vooral associëren met iets lichamelijks. *Psychische* pijn verschilt van lichamelijke pijn. Het kan samengaan met lichamelijke pijn, maar psychische pijn kan ook bestaan zonder dat er sprake is van lichamelijke pijn. In de literatuur worden verschillende woorden gebruikt om naar psychische pijn te verwijzen: mentale pijn, emotionele pijn, lijden. Maar ook woorden die zich minder makkelijk laten vertalen zoals *anguish* en *psychache*. Gelet op de grote variatie in verwijzingen naar psychische pijn bestond het eerste deel van deze promotie uit een conceptanalyse. De resultaten van die analyse zijn beschreven in hoofdstuk 2. Verschillende modellen en theorieën zijn systematisch met elkaar vergeleken, waarna geconcludeerd kon worden dat ze hetzelfde onderliggende fenomeen beschreven. In dit proefschrift wordt voor dat fenomeen de term 'psychische pijn' gebruikt. In het Engels wordt de voorkeur gegeven aan *psychological pain* in plaats van *psychic pain,* om een associatie met het paranormale te voorkomen. Op basis van de conceptanalyse kon psychische pijn gedefinieerd worden als 'een langdurig, onhoudbaar en onplezierig gevoel dat voortkomt uit het negatief beoordelen van een eigen onvermogen of gemis'.

Een formele definitie geeft richting aan wetenschappelijk onderzoek en de klinische praktijk. Maar zo'n definitie is ook erg theoretisch en doet nauwelijks recht aan de ervaring van intens lijden die psychische pijn kan zijn. Psychische pijn is vaak het gevolg van een verlies, met name verlies van iemand die je dierbaar is, bijvoorbeeld als gevolg van overlijden of een scheiding, of een verlies van iets dat in een belangrijke behoefte voorziet (bijv. een baan, je gezondheid, autonomie, een thuis). Maar psychische pijn kan ook het gevolg zijn van een onvermogen om een belangrijke behoefte te realiseren (bijv. vriendschappen, een opleiding of baan) of een onvermogen

om jezelf te beschermen tegen beschadiging (lichamelijk, geestelijk, seksueel) of gevoelens van schaamte. Verlies en onvermogen zijn zeker van toepassing wanneer sprake is van chronische ziektes, zoals bijvoorbeeld depressie, posttraumatische stress, schizofrenie of multiple sclerosis. Deze aandoeningen maken een leven zoals je leefde onmogelijk, en ze kunnen doelen die je jezelf had gesteld soms permanent onbereikbaar maken.

Wetenschappelijk onderzoek heeft laten zien dat mensen met depressie vaak in hoge mate psychische pijn ervaren, en dat psychische pijn statistisch gezien sterk correleert met depressie en symptomen als hopeloosheid en suïcidale gedachten. Onderzoek naar psychische pijn wordt allengs meer omvattend, maar onze kennis omtrent specifieke biologische *markers* van psychische pijn is nog beperkt. Een biologische marker is een kenmerk van ons lichaam dat gemeten kan worden, zoals hartslag of de aanwezigheid van bepaalde hormonen in ons bloed, en waarvan bekend is dat het toe- of afneemt met het fenomeen waarin men geïnteresseerd is. Zo neemt het hormoon cortisol bijvoorbeeld toe naarmate men meer stress ervaart. De in hoofdstuk 3 beschreven literatuurstudie concludeerde dat de ervaring van psychische pijn mogelijk gepaard gaat met een asymmetrie in hersenactiviteit, met name minder activiteit rechts frontaal dan links. Asymmetrie in hersenactiviteit is dus een mogelijke marker van psychische pijn. Meerdere bronnen hebben daarnaast gesuggereerd dat er een link bestaat tussen activiteit in de rechter frontale cortex en het autonoom zenuwstelsel. Hartslagvariabiliteit, de normale variatie in de tijdspanne tussen twee opeenvolgende hartslagen, is een maat voor het functioneren van het autonoom zenuwstelsel. Hartslagvariabiliteit en frontale asymmetrie in hersenactiviteit vertegenwoordigen twee kanten van een theoretisch model (*circumplex model of affect*) dat emotie beschrijft aan de hand van het soort emotie (positief vs. negatief), ook wel emotionele valentie genoemd, en de fysiologische opwinding (*activation*) die met de emotie gepaard gaat.

Zowel hartslagvariabiliteit als frontale asymmetrie, met name met betrekking tot hersenactiviteit in de alfa-band (8 – 13 Hz) gemeten via een encefalogram (EEG), zijn uitgebreid onderzocht in rusttoestand in mensen met depressie. Gegeven de sterke link tussen depressie en psychische pijn was het doel van deze dissertatie om de relaties te verkennen tussen hartslagvariabiliteit, frontale asymmetrie in de alfa-band, en psychische pijn in volwassenen met depressie. Onder deze overkoepelende doelstelling zijn vier primaire doelen onderscheidden: (1) vaststellen of frontale alfa-asymmetrie een voorspeller (lees, een marker) is van psychische pijn nadat gecompenseerd is voor de mate van depressie, hopeloosheid, en suïcidaliteit, (2) vaststellen wat de richting is van de associatie tussen psychische pijn en frontale hersenactiviteit in frequentiebanden anders dan alfa, (3) vaststellen of hartslagvariabiliteit een voorspeller is van psychische pijn nadat gecompenseerd is voor de mate van depressie, hopeloosheid, en suïcidaliteit, en (4) vaststellen of alfa-asymmetrie en hartslagvariabiliteit zijn afgenomen na het invullen van vragenlijsten omtrent psychische pijn, vergeleken met een nulmeting. Daarnaast was er een secundair doel om studieresultaten verkregen met traditionele analysemethodes te vergelijken met resultaten verkregen met een methode genaamd *fractal dimension*, die is gebaseerd op niet-lineaire dynamische systeemtheorie.

De deelnemers aan deze studie waren volwassenen met depressie in hun anamnese. Dit betekent dat sommige deelnemers een depressieve episode doormaakten ten tijde van de studie, maar dat dit voor andere deelnemers langer geleden was. Na het invullen van vragenlijsten omtrent depressie, hopeloosheid, en suïcidaliteit, werd een nulmeting gedaan. Gedurende vijf minuten werden hartslag en EEG gemeten, waarbij de deelnemers rustig rechtop zaten met hun ogen gesloten. Hierna werden twee gevalideerde vragenlijsten ingevuld over psychische pijn: de *Psychache Scale* en de *Orbach & Mikulincer Mental Pain* (OMMP) questionnaire. Op het invullen van de vragenlijsten volgden vijf meetsessies van vijf minuten elk, waarbij op

dezelfde wijze hartslag en EEG werden gemeten. Tussen de sessies was steeds een korte pauze van enkele minuten, al naar gelang de behoefte van de deelnemer. De deelnemers werden gemiddeld bijna 7 jaar vóór deze studie voor het eerst gediagnosticeerd met een vorm van depressie. De gemiddelde leeftijd van de deelnemers was 35 jaar en vrouwen waren ruim in de meerderheid (75% tegenover 25%). Het nivo van psychische pijn dat de deelnemers rapporteerden was gemiddeld iets minder hoog dan is gerapporteerd voor patiënten die waren opgenomen voor een depressieve episode en ruim lager dan gerapporteerd in een studie onder vrouwen die een suïcidepoging hadden gedaan. Daarentegen was het nivo van psychische pijn aanzienlijk hoger dan in studies gedaan onder reguliere studenten. Voor klinische toepassing worden depressie en hopeloosheid geclassificeerd als minimaal, mild, matig of ernstig. Deelnemers in deze promotiestudie ervaarden gemiddeld een matig nivo van depressie en hopeloosheid.

Hoofdstuk 4 rapporteert over de eerste twee doelstellingen van de studie. Statistische correlaties tussen depressie, hopeloosheid, suïcidaliteit en psychische pijn gemeten op beide vragenlijsten waren overwegend sterk. Een regressiemodel biedt de mogelijkheid om de sterkte van de relatie tussen twee variabelen A en B te beoordelen, waarbij gecompenseerd kan worden voor de relatie tussen A en andere variabelen. Zo bleek dat er geen statistisch significant verband bestond tussen psychische pijn en frontale asymmetrie in de alfa-band als gecompenseerd werd voor het verband tussen psychische pijn, depressie en hopeloosheid. Anders gezegd, frontale alfa-asymmetrie had geen toegevoegde waarde boven depressie en hopeloosheid in het voorspellen van het nivo van psychische pijn. Wanneer daarentegen een asymmetrie op basis van *fractal dimension* in het regressiemodel werd gebruikt leverde dit wel een significante verbetering van de voorspelling op. Dit bleek alleen van toepassing voor psychische pijn gemeten met de OMMP. De analyse met betrekking tot de richting van associaties tussen psychische pijn en hersenactiviteit in frequentiebanden anders dan alfa, liet

zien dat activiteit in de delta-band (0,5 – 4 Hz) significant afnam met toenemende psychische pijn. Voor psychische pijn ervaren op het moment van invullen van de OMMP gold dit alleen voor delta-activiteit rechts frontaal. Voor de ergste psychische pijn die de deelnemers ooit hadden ervaren gold het voor frontale delta-activiteit in beide hersenhelften. Deze resultaten suggereren een verminderde rustactivatie van het zogenaamde *default mode network*, een hersennetwerk dat normaal meer activiteit vertoont naarmate het lichaam meer in rust is. Mogelijk dat meer psychische pijn samengaat met een verhoogde fysiologische opwinding (meer activatie) die samenhangt met het reguleren van emoties. De sterke afname van delta-activiteit bij toenemende 'ergste psychische pijn ooit', pijn die deelnemers waarschijnlijk ruim voor hun deelname aan de studie hebben ervaren, duidt op blijvende veranderingen in hersenactiviteit als gevolg van hevige psychische pijn. Het is echter niet gezegd dat deze veranderingen onomkeerbaar zijn.

Hoofdstuk vijf maakt een zijstap en beschrijft de relatie tussen hartslagvariabiliteit en psychische pijn, waarbij de deelnemers zijn gegroepeerd naar mate zij wel of niet antidepressiva gebruikten op het moment van de studie. Met betrekking tot hartslagvariabiliteit, psychische pijn, depressie, hopeloosheid en suïcidaliteit waren er geen verschillen van betekenis tussen de twee groepen. Een statistisch significant verband bestond tussen laagfrequente hartslagvariabiliteit (0,04 – 0,15 Hz) en psychische pijn in deelnemers die geen antidepressiva gebruikten, nadat gecompenseerd was voor de leeftijd van de deelnemers. Laagfrequente hartslagvariabiliteit nam af naarmate psychische pijn toenam. Voor de *fractal dimension* van de tijdspanne tussen opeenvolgende hartslagen werd een significante afname met toenemende psychische pijn aangetroffen voor deelnemers die wel antidepressiva gebruikten. De resultaten wijzen op verhoogde activiteit in de sympathische tak van het autonoom zenuwstelsel wanneer sprake is van grotere psychische pijn. Ook hier werden significante relaties alleen

aangetroffen voor psychische pijn gemeten met de OMMP en niet voor de *Psychache Scale*. Een lager nivo van hartslagvariabiliteit en van *fractal dimension* wordt beschouwd als een indicator van verminderde gezondheid.

Hoofdstuk zes gaat in op doelstelling nummer vier. De gedachte achter deze doelstelling is dat psychische pijn een onderwerp is waarover mensen niet licht spreken en dat het beantwoorden van vragen over psychische pijn een ernstige verstoring van de emotionele balans tot gevolg zou kunnen hebben. Vergeleken met de nulmeting, die werd gedaan voordat de vragenlijsten over psychische pijn werden ingevuld, waren hartslag en alfa-activiteit significant lager gedurende de vijf sessies die volgden. Er waren geen verschillen van betekenis in hartslagvariabiliteit en alfa-asymmetrie vóór en na de vragenlijsten. Dit suggereert dat het beantwoorden van vragen over psychische pijn geen blijvend negatief effect had op de deelnemers over de duur van de meetsessies. De resultaten wezen zelfs op een licht verbeterde emotionele toestand. Ander onderzoek heeft laten zien dat het benoemen van negatieve emoties (*affect labeling*) positief kan bijdragen aan het kunnen omgaan met die emoties. Mogelijk dat daarvan in deze studie eveneens sprake was. Dit betekent niet dat het beantwoorden van de vragen de deelnemers niets deed. In een subgroep van deelnemers (n = 13) zijn metingen gedaan tijdens het invullen van de vragenlijsten en daaruit kwam naar voren dat hartslag en laagfrequente hartslagvariabiliteit significant hoger waren dan de nulmeting, terwijl er geen verschil was in laagfrequente hartslagvariabiliteit tussen de metingen tijdens en na het invullen van de vragenlijsten. De psychische pijn ervaren in deze subgroep was eveneens significant hoger. Dit zou er op kunnen wijzen dat mensen die veel psychische pijn ervaren meer dan anderen negatief beïnvloed worden door het beantwoorden van vragen over psychische pijn.

In het laatste hoofdstuk waarin gerapporteerd wordt over de verzamelde data, hoofdstuk zeven, is gekeken naar verschillen in hartslagvariabiliteit en hersenactiviteit tussen deelnemers die wel of niet een

suïcidale behoefte voelden. Ook worden daar resultaten met betrekking tot doelstelling drie beschreven. De deelnemers die een suïcidale behoefte voelden hadden vaker dan de andere deelnemers meer dan eens een suïcidepoging ondernomen. Hun nivo van depressie, hopeloosheid en psychische pijn gemeten met de *Psychache Scale* was ook statistisch significant hoger. In regressiemodellen voor de groep zonder suïcidale behoefte bleek dat, als gecompenseerd werd voor depressie en hopeloosheid, zowel laagfrequente hartslagvariabiliteit als delta-activiteit rechts frontaal de voorspelling van psychische pijn gemeten met de *Psychache Scale* statistisch significant verbeterde. Voor de groep met suïcidale behoefte was dit niet het geval, mogelijk omdat het een relatief kleine groep was (n = 11). Suïcidale behoefte had geen effect op de voorspelling van psychische pijn gemeten met de OMMP of op ergste psychische pijn ooit. Deze resultaten wijzen op een mogelijk hogere gevoeligheid van de *Psychache Scale* dan de OMMP voor een onderliggende suïcidale behoefte samenhangend met psychische pijn. Dit is van belang als psychische pijn gemeten wordt met het oog op suïcidepreventie.

Op basis van deze promotiestudie kan worden geconcludeerd dat laagfrequente hartslagvariabiliteit en EEG delta-activiteit potentiële markers van psychische pijn zijn. Toekomstig onderzoek naar psychische pijn kan specifieke markers van de sympathische tak van het autonoom zenuwstelsel gebruiken om na te gaan of psychische pijn inderdaad varieert met sympathische activiteit zoals op basis van deze studie is gesuggereerd. Van belang is ook om na te gaan of het effect van aanhoudende psychische pijn op hersenactiviteit in de delta-band omkeerbaar is. Omdat psychische pijn niet beperkt is tot mensen met depressie of enig andere psychiatrische aandoening, is het belangrijk om onderzoek naar psychische pijn uit te breiden naar de algemene populatie.

Het verzachten en beheersbaar maken van pijn is een fundamentele taak van verpleegkundigen. Maar als het aankomt op interventies die

momenteel beschikbaar zijn om psychische pijn te verlichten, dan zijn de mogelijkheden beperkt. Laagfrequente hartslagvariabiliteit en hersenactiviteit, in de vorm van frontale delta-activiteit of *fractal dimension* asymmetrie, zijn uitermate geschikt voor gebruik in een interventie op basis van terugkoppeling. Daarbij wordt hartslag of hersenactiviteit ter plekke gemeten en direct zichtbaar gemaakt, en wordt de cliënt geleerd hoe dit te gebruiken om psychische pijn te verminderen. Deze promotiestudie heeft een stevige basis gelegd voor het ontwikkelen van een dergelijke interventie.

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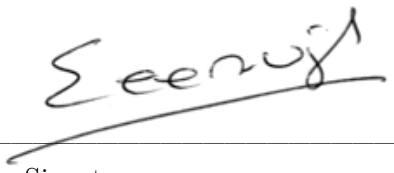

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