Thesis presented for the degree of Doctor of Philosophy
In the Faculty of Humanities

Human subjective homologues of established basic emotion correlations in lower mammals: A neuro-psychoanalytic study

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PNTELE001

In the Department of Psychology
University of Cape Town
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Supervised by:
Professor Mark Solms
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Declaration

I hereby declare that this submission is my own work, both in concept and execution, and that to the best of my knowledge and belief it contains no material written by another person nor material that has been accepted for the award of any other degree or diploma of the university or other institute of higher learning, except where due acknowledgment has been made in the text.

Eleni Pantelis

Signed by candidate

Date: 14 February 2019
I would like to thank all my participants. Thank you for trusting us and thank you for your commitment and enthusiasm. This study would never have happened without you.

I owe so much to my supervisor, Professor Mark Solms. Your support and guidance throughout this study was invaluable. I am sincerely grateful.

To my unofficial supervisor, Dr Susan Malcolm-Smith, I express my heartfelt thanks. You brought me to the finishing line.

To my friends and family, thank you for not letting me give up.

Thank you to the Hope for Depression Research Foundation who generously funded parts of this research.

This thesis is dedicated to Professor Jaak Panksepp (1943 –2017). You were the inspiration for this study. I am so sorry you did not get to see it to the end.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ADHD</td>
<td>Attention Deficit Hyperactivity Disorder</td>
</tr>
<tr>
<td>ANPS</td>
<td>Affective Neuroscience Personality Scale</td>
</tr>
<tr>
<td>ACC</td>
<td>anterior cingulate cortex</td>
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<td>ANS</td>
<td>autonomic nervous system</td>
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<tr>
<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
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<tr>
<td>BDNF</td>
<td>brain-derived neurotrophic factor</td>
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<tr>
<td>CRF</td>
<td>corticotrophin releasing factor</td>
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<tr>
<td>CREB</td>
<td>cAMP response element binding protein</td>
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<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
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<tr>
<td>DA</td>
<td>dopamine</td>
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<tr>
<td>DAT</td>
<td>dopamine transporter</td>
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<tr>
<td>DSM-5</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<tr>
<td>DTI</td>
<td>diffusion tensor imaging</td>
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<td>DBS</td>
<td>deep brain stimulation</td>
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<tr>
<td>DRN</td>
<td>dorsal raphe nucleus</td>
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<tr>
<td>DMN</td>
<td>default mode network</td>
</tr>
<tr>
<td>ECR-R</td>
<td>Experiences in Close Relationships-Revised</td>
</tr>
<tr>
<td>EPS</td>
<td>extrapyramidal symptoms</td>
</tr>
<tr>
<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
</tr>
<tr>
<td>GABA</td>
<td>Gamma-Amino Butyric acid</td>
</tr>
<tr>
<td>HPA</td>
<td>hypothalamic-pituitary-adrenal</td>
</tr>
<tr>
<td>ISA</td>
<td>introspective socio-affective</td>
</tr>
<tr>
<td>IL</td>
<td>interleuken</td>
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<tr>
<td>KOR</td>
<td>κ-opioid receptor</td>
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<tr>
<td>L-DOPA</td>
<td>Levodopa</td>
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<tr>
<td>mPFC</td>
<td>medial prefrontal cortex</td>
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<tr>
<td>M6G</td>
<td>morphine-6-glucuronide</td>
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<tr>
<td>ML-DA</td>
<td>mesolimbic dopamine</td>
</tr>
<tr>
<td>MFB</td>
<td>medial forebrain bundle</td>
</tr>
<tr>
<td>MCH</td>
<td>melanin-concentrating hormone</td>
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<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
</tr>
<tr>
<td>MAO</td>
<td>monoamine oxidase</td>
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<tr>
<td>MFB</td>
<td>medial forebrain bundle</td>
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<tr>
<td>MCP-1</td>
<td>monocyte chemoattractant protein-1</td>
</tr>
<tr>
<td>MOR</td>
<td>μ-opioid receptor</td>
</tr>
<tr>
<td>MDI</td>
<td>Major Depression Inventory</td>
</tr>
<tr>
<td>NA</td>
<td>negative affect</td>
</tr>
<tr>
<td>NMADA</td>
<td>nonselective N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NE</td>
<td>norepinephrine</td>
</tr>
<tr>
<td>NAc</td>
<td>nucleus accumbens</td>
</tr>
<tr>
<td>PA</td>
<td>positive affect</td>
</tr>
<tr>
<td>PANAS</td>
<td>Positive and Negative Affect Schedule</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s Disease</td>
</tr>
<tr>
<td>PAG</td>
<td>periaqueductal gray</td>
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<tr>
<td>PFC</td>
<td>prefrontal cortex</td>
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<tr>
<td>PTSD</td>
<td>post-traumatic stress disorder</td>
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<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
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<tr>
<td>SNRI</td>
<td>serotonin and norepinephrine reuptake inhibitors</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>STN</td>
<td>subthalamic nucleus</td>
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<tr>
<td>SAAM</td>
<td>State Adult Attachment Measure</td>
</tr>
<tr>
<td>TNF</td>
<td>tumour necrosis factor</td>
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<tr>
<td>TRD</td>
<td>treatment resistant depression</td>
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<tr>
<td>UCT</td>
<td>University of Cape Town</td>
</tr>
<tr>
<td>VS</td>
<td>ventral striatum</td>
</tr>
<tr>
<td>VTA</td>
<td>ventral tegmental area</td>
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Abstract

Early separation experiences predispose people to depression and depressive episodes are triggered by experiences of social loss. The normal separation response entails a 'protest' phase followed by a 'despair' phase. The affective neuroscience paradigm of Jaak Panksepp identifies two basic emotion systems as being centrally involved in this normal separation response, namely, PANIC/GRIEF and SEEKING, and it conceptualises the despair phase of the cascade as the normal prototype for depression. In affective terms, major depression is seen as a disorder characterised by an overactive PANIC/GRIEF system and an underactive SEEKING system. There is considerable pre-clinical research that underwrites this conclusion, but the evidence in humans is limited. The general aim of this thesis was to investigate the claim that the feelings associated with depression represent an abnormal variant of the normal mammalian separation response in human subjects. The PANIC/GRIEF and SEEKING systems were artificially stimulated and dampened in a sample of healthy volunteers (N=16) via the administration of opioid and dopamine antagonists and agonists. This was an exploratory study, with a double-blind, placebo-controlled, repeated-measures design. The effects of the medications on SEEKING, PANIC/GRIEF, positive and negative affect and mood were investigated using both quantitative and qualitative measures.

The results provided suggestive rather than strongly confirmatory evidence for the central hypotheses of this study. Naltrexone (a mu-opioid antagonist) did not increase PANIC/GRIEF and negative affect as predicted but there was some evidence that it led to the worsening of mood, a significant reduction in positive affect and feelings of social and affective disconnection. Morphine (a mu-opioid agonist) reduced PANIC/GRIEF as predicted, but contrary to predictions, positive affect was reduced. There was some evidence to show that Morphine led to an increase in the expression of feelings of contentment, relaxation, happiness and reduced concern. Haloperidol (a dopamine antagonist) reduced SEEKING as predicted but did not increase negative affect as expected. There was some evidence to show that it led to...
worsening of mood and positive affect and produced depressive affects such as low drive, low energy, loss of motivation and interest. Madopar (a dopamine agonist) did not increase SEEKING or improve mood as predicted, but there was some evidence that it generated positive affects and reduced the sadness associated with experiences of loss. On Haloperidol, participants with lower ‘despair’ had significantly reduced SEEKING and positive affect and higher depression scores, compared to participants with higher ‘despair’. On Madopar, participants with lower ‘despair’ experienced a greater improvement in positive affect and mood, compared to those with higher ‘despair’. On Morphine, measures of avoidant attachment rather than anxious attachment were comparatively more effective in differentiating between Low and High ‘protest’, and that those with higher ‘protest’ experienced comparatively more PANIC GRIEF, negative and depressive affect. These results provide some ‘proof of concept’ for the conceptualization of depression as pathological ‘despair’ and that depression feels bad because a dampened SEEKING system and a stimulated PANIC/GRIEF system produce the type of feelings that are characteristic of depression. The results also draw attention to factors that potentially contribute to the limited success of purely drug-focused interventions in depression.
There are long-standing claims that suggest that early separation experiences predispose people to depression, and that depressive episodes are triggered by experiences of social loss (Bowlby, 1969, 1973, 1980; Freud, 1917; Heim & Nemeroff, 1999). John Bowlby’s classical (1969) description of the normal separation response (assuming a pre-existing attachment bond) entails, first, a ‘protest’ phase, then, a ‘despair’ phase. In the first phase of this prototypical situation, the human child (like all mammals) emits distress vocalizations and searches for the mother; then, in the second phase, it gives up the search and becomes quiescent (quasi-hibernates). Research conducted within the ‘affective neuroscience’ paradigm of Jaak Panksepp (Panksepp, 1998) identifies two basic emotion systems as being centrally involved in this normal separation response, namely, PANIC/GRIEF\(^1\) and SEEKING\(^2\) (Panksepp & Watt, 2011a). At a ‘primary-process’ (unconditioned) level, the PANIC/GRIEF system regulates social attachments by generating negative affects following social separation and the SEEKING system generates a hedonic state of anticipatory expectation, promoting exploratory behaviour and, in the context of social separation, seeking reunification (Panksepp, 2003). The ‘protest’ phase is thus associated with aroused dopamine-mediated SEEKING, followed by the ‘despair’ phase, which is associated with kappa opioid mediated shutting down of this dopaminergic SEEKING (Panksepp & Watt, 2011a).

\(^1\)Panksepp uses this term as well as PANIC, SEPARATION-DISTRESS and SADNESS at different times to refer to the same system. The term PANIC/GRIEF is the one he uses most consistently, especially in his later writings. I will therefore follow this usage. Readers should be contextually aware, however, that at some points in this study, I am specifically focusing on the ‘panic’ component of this bi-phasic system.

\(^2\)The terms are capitalized in order to avoid confusion with the vernacular use of the same words and also to denote that they refer to core emotion systems that have been identified at a neural level.
These brain mechanisms of the separation-distress cascade have been investigated mainly in animal models. The protest phase is mediated by the activity of μ (mu)-opioids. There is substantial empirical support for the role of the opioid systems in the physiological regulation of hedonic experiences in animals and humans (Berridge, Robison & Aldrige, 2009). Also, empirically established in animal models (but less well known) is the mechanism by which the protest phase converts to despair (Panksepp & Watt, 2011a). A strong candidate for the brain mechanisms of despair is blockade of mesocorticolimbic D2-type activity through kappa opioid (dynorphin) inhibition of medial forebrain dopamine. Stress induces the release of dynorphin, which in turn activates kappa opioid receptors and down-regulates dopamine levels. Thus, prolonged social loss, as reflected by a highly activated PANIC system, diminishes SEEKING.

The assumption here is that the despair phase of the mammalian separation distress cascade is the normal prototype for depression, conceptualised as too easily provoked or excessively prolonged 'despair'. In affective terms, this translates to an understanding of major depression as a disorder characterised by an overactive PANIC/GRIEF system and underactive SEEKING system (Coenen, Schlaepfer, Maedler, & Panksepp, 2011; Panksepp, 2004). There is a substantial body of experimental work in animal models of depression which points to this conclusion (see Panksepp & Watt, 2011b for review), but the evidence in humans is limited. This is important, for the reason that animal models are just that: models. Animals lack the possibility of reporting subjective states of ‘despair’; that is, feelings of sadness, grief, etc. These states must be inferred in animal models.

In short, what is lacking in the human depression literature is an understanding of the neural mechanisms of ‘why depression feels bad’ (Solms & Panksepp, 2010). All depressed patients experience psychological distress. Most of the current lines of investigation into depression draw attention to factors of potential causal significance, but they do not provide
insight as to why depression *feels* as it does. Therefore, the aim of this thesis is to determine whether depression ‘feels bad’ because the brain mechanisms for SEEKING and PANIC/GRIEF generate the specific feelings which are typical of depression, such as mental pain, sadness, pessimism, hopelessness, anergia and anhedonia.

This thesis investigates the claim that the *feelings* associated with depression represent an abnormal variant of the normal mammalian separation response. Specifically, it asks the question: does an artificially stimulated PANIC/GRIEF system and dampened SEEKING system produce declarative depressive *affects* (the reportable human equivalents of ‘protest’ and ‘despair’ *behaviours*, respectively) in a sample of healthy volunteers?

In order to contextualize this research, the literature review that follows provides an overview of: (a) the empirical neuroscientific literature on depression; (b) Panksepp’s model of social attachment and associated emotion; and (c) the neurochemistry of the opioid and dopaminergic systems. There is a considerable body of knowledge on each of these topics and this review is not intended as a comprehensive summary, but rather focuses on aspects of the literature that are most pertinent to the question under investigation. The aim is to position this investigation within a theoretical framework that allows us to better understand how (and whether) depression might be conceptualized as pathological ‘despair’ – that depression may be considered an abnormal variant of the typical mammalian separation response.

If the neurochemistry of the mammalian separation response can be shown to underpin the feeling states that characterise (indeed, in a sense, constitute) human depression, then this research will not only provide ‘proof of concept’ but it might also lay the foundations for new approaches to the pharmacological treatment of depression.
CHAPTER TWO:
Literature Review

Major Depression

Dating back to classical times, portrayals of major depression, a condition previously referred to as melancholia, have appeared in accounts of human psychological suffering (Akiskal et al., 2000). While referent terms have changed over time, many of the key symptoms that inform modern diagnoses were recognized in the Hippocratic era, already, as was the acknowledgment of both mental and physical ailments in the symptom complex. Depression might as such be regarded as a prototypical human experience that transcends both time and culture, that is currently the leading cause of disability in many Western societies due to its profound disruption of social functioning (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006).

Epidemiology. Presently, Major Depressive Disorder (MDD) has been reported as one of the most common mood disorders in Psychiatric and Primary Care settings and is often accompanied by decreased physical and social functioning (Gili et al., 2014). There are approximately 350 million people worldwide with depression, and it is the leading cause of disability in the world (D’Souza & Jago, 2014). Prevalence estimates vary, from 3% in Japan to 16.9% in the U.S., but in most countries the disorder is common, with a frequency typically varying from 8% to 12% (Flint & Kendler, 2014). Epidemiological studies report that approximately ten percent of all individuals will develop this condition at some point in their life, and women are twice as likely as men to become depressed (Albert, 2015). Global prevalence rates are 5.1% for women and 3.6% for men (WHO, 2017).

Diagnosis. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) now recognises four main disorders: MDD, Dysthymia (now called Persistent Depressive Disorder), Disruptive Mood Dysregulation and Premenstrual Dysphoric
Disorder. The diagnosis of MDD requires that five (or more) of the following symptoms are present during the same two-week period, at least one of the symptoms being either (a) depressed mood; or (b) loss of interest or pleasure; significant changes in weight or appetite; insomnia or hypersomnia; psychomotor changes; fatigue; feelings of worthlessness or excessive or inappropriate guilt; diminished ability to think or concentrate, or indecisiveness; recurrent suicidal ideation (American Psychiatric Association, 2013). Although this diagnosis is atheoretical in principal, perhaps the most intriguing symptom with regard to the pathophysiology of depression is that previous editions of the DSM included a bereavement exclusion criterion for a major depressive episode that was applied to depressive symptoms lasting less than two months following the death of a loved one. The bereavement exclusion has now been omitted, one of the reasons cited is that “bereavement is recognized as a severe psychosocial stressor that can precipitate a major depressive episode in a vulnerable individual, generally beginning soon after the loss” (American Psychiatric Association, 2013, p. 811). This suggests an inherent link between depression and social loss.

Etiologies. Recent attempts to understand depression have emphasized the highly subjective nature of the diagnosis; no fixed objective criteria exist and the experience of MDD may therefore be extremely variable across individuals (Anisman & Matheson, 2005). Accordingly, criticism has mounted against the notion of depression as a discrete ‘illness’, rather than a heterogeneous syndrome (Nestler et al., 2002). Indeed, converging evidence from neuroimaging, biochemical, clinical and post-mortem studies have pointed to a highly complex systems-level disorder that is unlikely to be the result of a single neurochemical/anatomical brain disease (Mayberg et al, 2005; Nestler et al., 2002; Watt & Panksepp, 2009; Yohn, Gergues, & Samuels, 2017). Despite the dramatic surge in neurobiological research over the past few decades, a clear appreciation of the basic brain foundations of MDD remains elusive and the mechanisms underpinning depression are still
poorly defined. Many hypotheses of depression have been introduced through antidepressant
drug/medication research. However, the rationales of these hypotheses often follow from
pharmacological manipulations in depressed patients (based in serendipitous drug discovery)
and are not necessarily based on a theoretical conceptions of the pathophysiology of the
disease. Depression research has focused largely on the physical correlates of depression,
such as neurotrophic changes, rather than the brain mechanisms of depressive affect and
behaviour itself. What follows is a brief account of some of these current hypotheses.

Studies suggest that while genetic factors appear to be substantial in the etiology of
MDD, accounting for up to 37% in heritability, genetics alone do not affirm the veracity of
any particular biological theory (Flint & Kendler, 2014). Even if heritability features strongly
in the etiology of MDD, a true ‘depression gene’ (Krishnan & Nestler, 2008) has not been
identified, and life events account for a substantial variance in vulnerability (Sullivan, Neale,
& Kendler, 2000). The gene encoding for the serotonin transporter (5-HTT) has been
associated with neuroticism and susceptibility to depression (Bufalino, Hepgul, Aguglia, &
Pariante, 2013; Canli & Lesch, 2007; Caspi et al., 2003; Levinson, 2006) but subsequent
studies have reported non-specific results. A meta-analysis conducted by Risch et al. (2009)
did not support the association between the risk of depression and this particular gene variant.

Epigenetic research has focused on two chromatin-modifying actions, DNA methylation
(Goud-Alladi, Etain, Bellivier, & Marie-Claire, 2018), and histone acetylation, implicated in
emotional processing and social defeat, respectively (Krishnan & Nestler, 2008). Drugs that
increase histone acetylation, such as, glyceryl triacetate and l-acetylcarnitine, are being
evaluated for their efficacy in psychiatric disorders (Peedicayil, 2018). Studies involving
genotype-guided antidepressant treatments have identified the following genes as particularly
relevant: SLC6A4, HTR2A, ABCB1 and cytochrome P450 genes (Fabbri & Serretti, 2015).

One of the major drawbacks of genetic studies (linkage and candidate gene association
studies, as well as more recent genome-wide association studies) is that these studies require very large sample sizes (around 10,000 or more cases and controls) to achieve sufficient power to detect effects. In small samples with unmatched phenotypes, there is also an increased risk of false-positive findings. Furthermore, the possible heterogeneity of depression has been argued to be a major stumbling block to significant findings, in that similar symptoms might arise from different disorders, or different gene-environment interactions may lead to the same disorder. To illustrate, Bosker et al. (2011) used data from the ‘Genetic Association Information Network genome-wide association study’ (p. 516), to investigate candidate gene and single-nucleotide polymorphism (SNP) associations that have previously been reported in MDD. They could only identify four significant candidate genes, out of a possible 55 candidate genes that had previously been reported in the literature to be associated with MDD. They were, C5orf20, NPY, TNF, and SLC6A2. However, more importantly, the authors argued that even their four significant findings could be false-positives, because of possible publication bias, previously reported false-positive findings, heterogeneity of the MDD phenotype and differences in contextual genetic or environmental factors.

With regards to neural circuitry, dysfunctional changes within certain brain regions and circuits that regulate emotion and reward have been implicated in depression. Three popular models of the neural circuitry involved in MDD include the limbic-cortical, cortico-striatal, and default mode network models. A meta-analytic study by Graham et al. (2013) reviewed functional magnetic resonance imaging (fMRI) evidence in support of these three models and found stronger evidence for the limbic-cortical and cortical-striatal models than for the default mode network model. Furthermore, they suggested that associated subcortical regions may act as trait vulnerability markers, whereas the more frontal cortical areas may act as state markers of MDD. A meta-analytically informed network analysis of resting state
fMRI identified a depression-related introspective socio-affective (ISA) network that partially overlaps with the default mode network model. The ISA network included hyperconnectivity among areas similar to those of the default mode network that may contribute to altered introspection and rumination in depression (Schilbach et al., 2014). The ISA network also contained additional depression-related areas, such as those involved in the processing and regulation of emotions. Lui et al. (2011) also used resting state data to investigate depression, but they compared patients with refractory and nonrefractory MDD. They found that disrupted functional connectivity in the thalamo-cortical circuits was related to refractory depression, whereas more distributed reductions in connectivity of the limbic-striatal-pallidal-thalamic circuit were related to nonrefractory depression. Korgaonkar, Fornito, Williams, and Grieve (2014) used diffusion tensor imaging (DTI) to investigate the structural changes in brain networks related to MDD, and found alterations in the structural connectivity between nodes of the frontal-thalamo-caudate regions and the default mode network.

Much of the current research on the neural circuitry of depression seems to involve various loops between the cortex, basal ganglia, limbic system and thalamus, as well as the default mode network, but these different circuits appear to link to different aspects of depression. In this regard, Foti, Carlson, Sauder, and Proudfit (2014) reported that MDD was associated with reduced reward-related neural activity but only in a subgroup of MDD patients with impaired mood reactivity to positive events. They argued that MDD was associated with dysfunction in multiple aspects of reward processing, that is, the primary characteristic in some cases of MDD may be a deficit in opioid-mediated “liking”; in other cases a deficit in dopamine-mediated “wanting” or learning (Berridge & Kringelbach, 2015). Morgan, Olino, McMakin, Ryan, and Forbes (2013) found that reduced striatal and enhanced medial prefrontal responses to reward to be particularly predictive of depressive symptoms in adolescents. Familial risk for MDD has been characterized by the dysregulation of affective
circuits for evaluating salient emotions (Watters, Korgaonkar, Carpenter, Harris, Gross, & Williams, 2018). Anhedonia has been shown to correlate with reduced connectivity of the ventral caudate to the dorsolateral prefrontal cortex, the parietal and temporal cortices and enhanced connectivity with the occipital cortex (Yang et al., 2017). Certain neural correlates of depression have been identified. Reductions in grey-matter volume and glial density in the prefrontal cortex and hippocampus are associated with depression (Krishnan & Nestler, 2008). Functional abnormalities in the amygdala and subgenual cingulate are correlated with negative emotions (Drevets, 2001) and stimulation of the dopaminergic nucleus accumbens (NAc) has been shown to have ameliorative effects in refractory depression (Schlaepfer et al., 2008). Increased amygdala, insula and ventrolateral prefrontal cortex activation in response to social exclusion has been reported in subjects with MDD (Kumar, Waiter, Dubois, Milders, Reid, & Steele, 2017).

The popular *monoamine hypothesis* posits that depression involves low levels of 5-HT, norepinephrine (NE), and/or dopamine (DA) levels in the CNS. It has been the prevailing hypothesis for several decades and originated from mechanistic studies of the serendipitously discovered tricyclic antidepressants and monoamine oxidase (MAO) inhibitors. Selective serotonin and norepinephrine reuptake inhibitors (SNRIs) remain first line treatments for MDD (Dale, Bang-Andersen, & Sánchez, 2015). There are numerous findings in support of this hypothesis: drugs that deplete serotonin and other catecholamines can lower mood (Ruhé, Mason, & Schene, 2007); reduced serotonin levels (through tryptophan depletion) can alter emotional processing and lower mood in individuals with a vulnerability to MDD (Fukuda, 2014; Roiser et al., 2009); there are reported changes in the functional connectivity of the raphé during tryptophan depletion (Salomon et al., 2011; Weinstein et al., 2015); reported reductions in serotonin transporter (SERT) binding in key limbic regions in depression (Kambeitz & Howes, 2015); and clinical trials demonstrating the
benefit of SSRIs in MDD (Fournier et al., 2010). MDMA (which has the highest efficacy for 5-HT release via SERT) in post-traumatic stress disorder (PTSD) is being implicated as a potential rapid-onset antidepressant (Patel & Titheradge, 2015). Even though SSRIs and MAO inhibitors are strong antidepressant agents, a meta-analysis conducted by Fournier et al. (2010) showed that true drug effects (defined as an advantage of antidepressant medication over placebo) were negligible for depressed patients with mild to moderate baseline symptoms, and were only noticeable in patients with very severe symptoms. According to the STAR*D report (Rush et al., 2006), approximately 50% of patients went into clinical remission after two treatment steps with SSRIs/SNRIs. For four consecutive treatment steps, the overall cumulative remission rate was 67%, leaving a large group of patients who responded inadequately to treatment. In an overview by Khan and Brown (2015), it was reported that the effect size of clinical depression trials was only 0.30, and when comparing data from industry (pharmaceutical) and non-industry clinical trials, the extent of reported symptom reduction on placebo was higher in non-industry trials. Furthermore, not all depressed patients exhibit serotonergic inconsistencies (Jans, Riedel, Markus, & Blokland, 2007) and there are studies that show that monoamine depletion does not affect mood in normal controls (Delgado & Moreno, 2000; Ruhe et al., 2007). It has also been demonstrated that critically low levels induced by tryptophan depletion does not cause depression in healthy subjects (Neumeister et al., 1997). The therapeutic response to SSRIs/SNRIs is often delayed (Dale et al., 2015) and the monoamine hypothesis fails to explain this latency of response (Boku, Nakagawa, Toda, & Hishimoto, 2018). Moreover, many antidepressants have adverse side-effects, such as nausea and sexual dysfunction (Anderson, Pace, Libby, West, & Valuck, 2012). Thus, although both noradrenergic and serotonergic systems are implicated in depression, the exact nature of the correlation with affective states remains unclear (Watt & Panksepp, 2009). Neither norepinephrine nor serotonin appear to be “the
final common pathway for the therapeutic effect of antidepressant drugs” (Delgado & Moreno, 2000, p.5) and depression is not simply a result of a “serotonergic vulnerability” or a neurotransmitter deficiency state (Krishnan & Nestler, 2008; Watt & Panksepp, 2009).

According to the neurotrophic hypothesis of depression, reduced levels of certain neurotrophic factors predispose to depression and an increase in these levels can have antidepressant effects (Zhang, Li, Sha, & Bu, 2015). Neurotrophic factors that have been linked to depression include brain-derived neurotrophic factor (BDNF; Koziek, Middlemas, & Bylund, 2008; Molendijk et al., 2014), glial cell line-derived neurotrophic factor (Lin & Tseng, 2015), insulin-like growth factor, vascular growth factor (VGF; Tseng, Cheng, Chen, Wu, & Lin, 2015), fibroblast growth factor (Borroto-Escuela et al., 2012), neurotrophin-3 (NT3), and nerve growth factor (NGF; Chen et al., 2015). However, research findings have not been consistent and meta-analytic methods are being employed more regularly in an attempt to review the evidence for and against these neurotrophic factors. BDNF seems to be one of the most popular neurotrophic factors currently linked to depression (Zhang et al., 2015). Research has demonstrated that several forms of stress reduce BDNF mediated signalling in the hippocampus and that long-term use of antidepressants could reverse neuronal atrophy and cell loss (Duman & Monteggia, 2006; Nibuya, Morinobu, & Duman, 1995; Sheldrick, Camara, Ilieva, Riederer, & Michel, 2018). However, these findings are once again not consistent, and, in some cases, the opposite effect has been shown, that is, that stressors can increase BDNF levels in the hippocampus (Groves, 2007). Haase and Brown (2015) suggest a reciprocal regulatory mechanism between serotonin and BDNF that contributes to neuronal activity homeostasis in the hippocampus, prefrontal cortex and other brain regions. According to their model, this homeostasis may be disrupted by long-term inflammatory responses, with subsequent negative effects on the survival and maintenance of neurons and dendrites in the hippocampus and the development of depressive symptoms.
From a *neuroendocrine* perspective, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is implicated in the pathophysiology of depression (Horowitz & Zunszain, 2015; Martinac et al., 2014), as it coincides with depressive episodes and partially reverses after successful treatment (Fassbender et al., 1998). Hypercortisolemia in depression can be demonstrated at several levels: (a) impaired glucocorticoid-receptor-mediated negative feedback (Brown, Varghese, & McEwen, 2004), this theory posits that abnormally high activity in the HPA axis, as a result of chronic stress, may result in excess cortisol production and subsequent depression-related neuropathology in susceptible individuals; (b) adrenal hyper-responsiveness to circulating adrenocorticotrophic hormone (ACTH; Parker, Schatzberg & Lyons 2003); and (c) hypersecretion of corticotrophin releasing factor (CRF; Arborelius, Owens, Plotsky, & Nemeroff, 1999; Nemeroff & Owens, 2002; Ogłodek, Szota, Just, Moś, & Araszkiewicz, 2014) where CRF and ACTH affect the metabolism of neurotransmitters and cortisol decreases tryptophan availability, impacting the synthesis of serotonin. Some findings suggest that hypercortisolemia is mostly found in inpatients and that the in/outpatient distinction is relevant to the presence of endocrine changes in major depression (Brouwer et al., 2005). In this regard, Herane-Vives et al. (2018) reported higher cortisol levels in severely depressed outpatients displaying melancholic features. Evidence from preclinical studies shows that exposure to episodes of severe separation distress in early life results in lasting changes to HPA axis and upregulation of CRF and could lead to a phenotype that is more vulnerable to stress and depression in adulthood (Heim & Nemeroff, 1999; Heim, Newport, & Mletzko, 2008). Moreover, different configurations of depressive symptoms may be related to different HPA-axis dysfunctions (Blatt & Luyten, 2009; Juruena, Bocharova, Agustini & Young, 2018). In this regard, hypercortisolemia may be linked to melancholic depression and HPA hypoactivation to atypical depression (Tofoli, Von Werne Baes, Martins, & Juruena, 2011).
Another approach to understanding the pathophysiology of depression is to consider the mechanisms of allostasis in response to stress. Several resilience factors have been identified in animal models: stress-induced upregulation of the transcription factor ΔFOSB inhibits stress-induced release of substance P, thereby promoting active defense responses (Berton et al., 2007); increased excitability of ventral tegmental area DA can moderate vulnerability to development of social avoidance (Krishnan et al., 2007); and the release of neuropeptide Y onto amygdala neurons produces resilient behavioural responses (Sajdyk et al., 2008).

*Overactive immune system* functioning is often observed in depressed individuals (Dantzer, 2009; Horowitz & Zunszain, 2015). Proinflammatory cytokines can produce the types of neurological changes that are commonly associated with depression, such as monoamine system changes, decreased neurogenesis, neurodegeneration, and regional brain abnormalities (Miller, Maletic, & Raison, 2009). The cytokine theory of depression evolved from findings showing that (a) there is an increased incidence of depression in patients with medical illness; (b) there are overlaps between depression and cytokine-induced sickness behaviour; (c) depression can be induced via stimulation of cytokine production; and (d) that the reduction of cytokine levels has antidepressant effects. Interestingly, Miller and Cole (2012) found that childhood adversity promotes a phenotype in which depression and inflammation co-occur. However, studies reporting on the neuroimmune interactions of increased cytokine in depression can be highly variable (Glassman, 2007). In their review article, Dunn, Swiergiela, and de Beaurepaire (2005) concluded that although immune activation and cytokines feature in depressive symptoms in some patients, cytokines are not essential mediators of depression. In a review of the inflammatory biomarkers of depression, patients with depression have been shown to have increases in peripheral levels of proinflammatory cytokines interleukin (IL)-6, IL-1β and tumour necrosis factor (TNF) (Han
Moreover, polyunsaturated fatty acids (PUFAs), glucocorticoids, gut microbiota and microglia have also been implicated in inflammation and depression alike (Ma et al., 2017). These findings have been fairly consistent, but are not always present because of the heterogeneity of depression. Another review by Young, Bruno, and Pomara (2014) report elevated serum levels of TNF-α, IL-1, IL-6, monocyte chemoattractant protein-1 (MCP-1) and C-reactive protein in depressed patients. Results were more mixed with regards to cerebrospinal fluid (CSF) levels of IL-6 and MCP-1 and IL-8 serum levels. Despite the demonstrated relationships between proinflammatory cytokines and depression, research has thus far not been able to identify cytokines that are highly specific to MDD. Eyre, Stuart, and Baune (2014) suggest that immune factors beyond pro- and anti-inflammatory cytokines come into play during different phases of depression, such as macrophages, astrocytes and microglia.

The glutamate hypothesis of depression posits that excitatory transmission of glutamate plays a key facilitatory role in the emotional and cognitive changes associated with depression. In their review, Sanacora, Treccani, and Popoli (2012) emphasise how cognition and emotion are largely mediated by glutamate synaptic transmission. Furthermore, they reported that there is compelling evidence to suggest that glutamate transmission is abnormally regulated in several limbic/cortical areas in depressed individuals and that atypical glutamatergic signalling is related to maladaptive changes in the function of excitatory circuitry. In addition, preclinical data has shown that environmental stress can alter synaptic transmission in limbic/cortical areas. Changes in plasma and CSF levels of glutamate, brain glutamate and glutamine levels have been found in patients with MDD, but results are inconsistent (Dale et al., 2015). Reduced levels of glutamate levels in the anterior cingulate have been reported in subjects with unipolar and bipolar depression (Wise et al., 2018). Ketamine (Zarate et al., 2006) and scopolamine (Furey, Khanna, Hoffman, & Drevets,
2010) in particular have been shown to produce rapid antidepressant actions and the development of nasal ketamine is being fast tracked by the FDA (Lapidus et al., 2014). Their actions are related to the reversal of synaptic atrophy caused by stress and depression which in turn leads to the reconnection of cortical-limbic circuits, lending support to the hypothesis that changes of neuroplasticity, that result in functional disconnections, might underlie the pathophysiology of depression (Duman, 2014). Other potential glutamatergic agents being investigated are: the nonselective N-methyl-D-aspartate (NMDA) antagonist, lanicemine (Zarate et al., 2013); the GluN2B selective antagonist, MK-0657 (Ibrahim et al., 2012); rapastinel (Burgdorf et al., 2013); 4-Cl-KYN (Zanos et al., 2015) and Gamma-Amino Butyric acid (GABA)-A alpha-5 (Gerhard, Wohleb, & Duman, 2016).

According to the adrenergic-cholinergic imbalance hypothesis of affective disorders, depression is associated with cholinergic hyperactivation and as a consequence of decreased noradrenergic activity (Janowsky, el-Yousef, Davis, & Sekerke, 1972). In particular, the muscarinic cholinergic receptor system is implicated in depression. Specifically, muscarinic receptor supersensitivity in depressed individuals (Riemann et al., 1994) and type 2 muscarinic (M2) cholinergic receptor gene (CHRM2) associations with increased incidence of unipolar depression and abnormal decreases in M2 receptor binding in bipolar depression (Comings et al., 2002). Numerous clinical and preclinical studies have shown that decreasing acetylcholine transmission at specific nicotinic acetylcholine receptors has a positive effect on mood (Mineur & Picciotto, 2010).

The co-occurrence of depression and type 2 diabetes, and of depression and coronary disease, has given rise to the hypothesis that lipid metabolism disturbances may be involved in the pathogenesis of depression (Puiu, Manea, Frunza, & Manea, 2014). Studies have investigated various components of lipid metabolism and have proposed different mechanisms for their relationship to depression, such as changes in cell membrane fluidity
with subsequent effects on serotonergic transmission, HPA axis and autonomic nervous system (ANS) dysfunction, higher levels of inflammatory markers, and Leptin resistance (to name a few). Research findings have varied, however, and it is not yet clear whether depression is a risk factor for lipid metabolism disturbances or whether these disturbances may increase the risk of depressive symptoms. Recent research found that middle-aged depressive patients with suicidal behaviour were more likely to have glucose and lipid metabolism disturbances, as well as insulin resistance (Koponen, Kautiainen, Leppänen, Mäntyselkä, & Vanhala, 2015). A longitudinal study of ageing found that the association between glucose metabolism (diabetes) and depressive symptoms was bidirectional in individuals aged 52 to 64, but not in those 65 years and older (Demakakos, Zaninotto, & Nouwen, 2014).

The following are all additional targets for depression research and could produce further pathophysiological insights and treatment advances. Melanin-concentrating hormone (MCH): SNAP-7941, a selective, high-affinity MCH1 receptor antagonist has been shown to produce antidepressants effects in preclinical models of depression (Borowsky et al., 2002; Schmidt et al., 2015). The orexigenic hormone, ghrelin, could act as a possible mediator of the adverse effects of stress on behaviour (Bali & Jaggi, 2015; Ishitobi et al., 2012; Lutter et al., 2008; Murgatroyd, Peña, Podda, Nestler, & Nephew, 2015). The orexin system has also been implicated in maternal care (D'Anna & Gammie, 2006) and depressive behaviour (Nollet & Leman, 2013). Low levels of the adipocyte hormone, leptin, have been associated with depressive behaviours in preclinical and clinical studies (Haleem, 2015; Lu, Kim, Frazer, & Zhang, 2008). The preclinical data demonstrating the role of Neuropeptide Y1 and Y2 receptors in emotional responses and stress is robust. In human studies, Neuropeptide Y plays a role in “buffering” the negative effects of stress (Fu, Acuna-Goycolea, & van den Pol, 2004; Morales-Medina, Dumont, & Quirion, 2010; Treutlein et al., 2017).
Undoubtedly, much progress in this field has been made, yet the shortcomings of the current research paradigms are exemplified by a number of conflicting clinical and neurophysiological findings. For example, although the influence of monoaminergic transmission in the modulation of emotion is well-established, there is no direct evidence for a causal relation between depression and monoaminergic dysregulation (Dale et al., 2015). The ardent focus on SSRIs as targets for efficacious treatment is possibly misleading since serotonin exerts widespread modulatory effects on the brain with modest overall efficacy as reported by the STAR*D findings (Rush, 2007). Approximately one-third of people diagnosed with depression do not respond to two or more of preferred SSRI treatments and are labelled treatment resistant (Trivedi et al., 2006). Moreover, anhedonia—a core symptom of depression—is often not alleviated with SSRIs. Interestingly, when the DA system is co-targeted, as with triple reuptake inhibitors (for example, DOV 216,303; Korte et al., 2015), antidepressant treatment seems to be more effective (Prins et al., 2012). In light of the variable resistance and delayed onset of monoamine-targeted antidepressants, Hasler (2010) proposes that monoaminergic dysfunction in MDD may represent the subsequent effects of other core abnormalities. Even stress, while most certainly a major contributing factor in the development of a depressive episode, is unsatisfactory as a simple casual mechanism since many individuals do not become depressed after excessive exposure to stress (Nestler et al., 2002), and moreover, intense stressful experiences have been linked to many psychiatric conditions, particularly, PTSD. Many people treated for MDD show no HPA dysfunction (Belmaker & Agam, 2008) and drugs targeting the HPA axis have not consistently shown antidepressant effects. There is likewise no concrete evidence in humans for the specific neurobiological mechanisms of the neurotoxic and neurotrophic hypotheses of depression (Hasler, 2010). Similarly, although there has been evidence of reduced CNS GABA in MDD patients since the 1980s (Hasler et. al, 2007; Romeo, Choucha, Fossati & Rotge, 2018), there
is also data to suggest that increases in GABA neurotransmission leads to negative mood (Levinson & Devinsky, 1999), and that a reduction in some aspects of GABA neurotransmission improves mood (Pehrson & Sanchez, 2015). Moreover, fluoxetine and vortioxetine (both effective serotonergic antidepressants) have opposite effects on GABA neurotransmission (Alvarez, Perez, & Artigas, 2014; Pehrson & Sanchez, 2015). This evidence all points to the fact that a simple reduction in GABA neurotransmission is not likely at the root of MDD. Furthermore, despite the numerous drugs under investigation that target the glutamate system, the specificity with regards to depression is questionable as glutamate is involved in almost every brain activity (Hasler, 2010). Elevated cytokine levels are implicated in the pathophysiology of depression but not all depressed patients have neuroinflammation (Bhattacharya, Derecki, Lovenberg, & Drevets, 2016). In studies identifying areas that correlate with depression and its symptoms, it is unclear whether the neural circuitry is altered as a consequence of depression or whether depression is a consequence of these alterations. Findings are inconsistent and confounded by comorbid diagnoses, with limited success in demonstrating cause-effect relationships. Lastly, a possible reason for the limited success of genetic studies could be that a diagnosis of depression typically relies on current classification criteria from the DSM or ICD-10 that are based on the presence of a cluster of symptoms. These clusters of symptoms do not necessarily refer to a homogenous disorder and therefore the current classification criteria of depression do not conform to genetically relevant phenotypes (Hasler, 2010).

**Conceptual Foundations of the Affective Model of Depression**

The present thesis is grounded in the affective neuroscience model of depression. What follows below are descriptions of several foundational principles on which this model of depression is conceptualized.
Depression is about feelings. It is evident from the many novel targets of therapeutic intervention currently under investigation that depression is a heterogeneous syndrome. There is no current treatment that has proven to be effective in all clinically depressed patients, reinforcing the view that depression may consist of etiologically distinct subgroups. Typically, subgroups of depression are either classified according to their clinical symptomology or identified on a pathophysiological basis. What is arguably more generalizable is the underlying affective state of depression. In other words, what is common to all depressed patients is that they experience psychological pain and/or hopelessness. Most lines of investigation into depression discussed above draw attention to factors of potential causal significance, but do not provide any insight into why depression feels the way it does. Although the predominant classification is one of symptomology, depression for the individual sufferer is a complex and subjective experience which has meaning. The symptoms of depressed affect, like low self-esteem, low motivation, hopelessness and anhedonia, signify a loss of expectant interest in the real world. In depressed adolescents, the presence of anhedonia is a significant predictor of poor recovery (McMakin et al., 2012).

This leads us to the introduction of one of the first conceptual principles central to this research: Depression is about affect, and yet the underlying mechanisms of the subjective experience of the psychological pain and despair of depression remain largely unexplored. I argue that the relative lack of neuroscientific investigation into depressive affect has left a significant gap in our understanding of depression because the psychological essence of the felt experience is arguably the common denominator. It is surely not fortuitous that irrespective of the type or duration of the depressive state, it consistently feels bad. This must have biological significance.

Moreover, it is not mere coincidence that the core criteria of the DSM conceptualise MDD as primarily a ‘felt disorder’ (low mood, low self-esteem, loss of motivation, guilt, loss
of pleasure and so on). Without these feelings present, a patient is not likely to be diagnosed with depression. And yet, there has been a great hesitancy on the part of the general neurosciences to approach the subjective aspect of depression as a fundamental symptom for guiding research. This neglect is arguably a repercussion of archaic behaviouristic principals, which limit scientific inquiry to tangible, observable events; but, as Solms (2011) argues, to deny the causal contribution of subjective feelings in the behavioural and cognitive components of depression is to deny the very nature of the disorder itself. Certainly, a bereaved individual can look very much like a case of clinical depression, a resemblance that was cordially noted in the DSM-5 criteria; a resemblance that was also previously recognised by Freud (1917) who considered melancholia (depression) to be a pathological product of mourning (grief). Freud observed that symptoms such as sadness, loss of appetite, disturbed sleep and withdrawal from social activities were similar in depressed individuals and those suffering from a loss of a loved one. The purpose of including this differential diagnostic criterion was therefore precisely because bereavement could be mistaken for depression, since many of the symptoms of depression resemble that of bereavement. Symptoms such as anhedonia, low mood, guilt, sleep disturbance and occasionally suicidal ideation may be present in both conditions (Iglewicz, Seay, Zetumer, & Zisook, 2013).

This bereavement exclusion criterion has been removed from the DSM-5 for the reason that (a) “bereavement is recognized as a severe psychosocial stressor that can precipitate a major depressive episode in a vulnerable individual”, and (b) “evidence does not support the separation of loss of a loved one from other stressors in terms of its likelihood of precipitating a major depressive episode” (APA, 2013a, p.5).

This acknowledgement introduces and in fact reinforces a further basic principle of the affective neuroscience model of depression, which is that there is an entailment in depression of the brain mechanisms of social loss.
**Love is an attachment.** Attachment theory presupposes an innate bonding system, presumably analogous with the attachment circuitry in other mammals, that operates to keep infants near their caregivers in the presence of threats and to modulate seeking support when necessary (Nelson & Panksepp, 1998). This system continues to regulate social interactions in intimate relationships into adulthood (Hazan & Shaver, 1987). Adult attachment styles typically vary on the dimensions of anxiety and avoidance (Brennan, Clark, & Shaver, 1998; Fraley, 2002). Differences in adult attachment have been shown to modify the activation of corticolimbic circuits in response to social and emotional stimuli, to the extent that an anxious attachment style seems to increase the responsiveness of brain circuits to negative social cues, and an avoidant attachment style lowers responsiveness to socioemotional processing (Vrticka, Sander, & Vuilleumier, 2012). More importantly, high avoidant attachment (as measured by the Experiences in Close Relationships-Revised (ECR-R)) has been associated with low μ-opioid receptor (MOR) availability in areas that form part of the social distress circuit (Nummenmaa et al., 2015). These findings correspond to the animal research that has established how the opioid system modulates bonding and attachment in other mammals (Nelson & Panksepp, 1998).

**Separation hurts.** According to attachment theory, attachment styles reflect mental representations about the primary caregiver and the self; representations not only about the care received but the worthiness to receive it (Bowlby 1969). These representations, established in childhood, are considered to be stable and can be triggered during episodes of distress (Mikulincer & Shaver, 2007). There is an abundance of literature in animal models that provides evidence that early adverse experience such as the separation distress following prolonged maternal separation can lead to structural and functional changes in an interconnected network of brain regions that are involved in neuroendocrine control, autonomic regulation and emotional regulation. Such changes translate into an integrated...
network failing to compensate adequately for additional stressors in adult life and manifesting in behavioural and physiological changes that form the clinical phenotype of depression (Lupien, McEwen, Gunnar, & Heim, 2009; Slavich, Monroe, & Gotlib, 2011). From this perspective, depression has been conceptualised as an “inappropriate adaptation to stress” (Bali, Singh, & Jaggi, 2014, p.347), and Panksepp and Watt (2011a) argue that chronic stress (i.e. separation distress) may be the “gateway” into depression, since depression and separation-distress share neurobiological and emotional characteristics.

The historic human literature recognizing the precipitating effect of social loss on depressive episodes is extensive (Bowlby, 1969, 1973, 1980; Freud & Burlingham, 1944; Spitz, 1946). Childhood adversities and early life stress are consistently associated with an increased risk of initial onset of depressive episodes (Hovens, Giltay, Spinhoven, van Hemert, & Penninx, 2015) and constitute a major risk factor for the subsequent development of depression (Charney & Manji, 2004; Post, 1992). The structural and functional changes following early life stress episodes are similar to those seen in adults with depression (Anda et al., 2006; Kaufman, Plotsky, Nemeroff, & Charney, 2000). Alterations include glucocorticoid resistance; increased levels of inflammation; increased CRH activity; decreased oxytocin activity (Danese et al., 2011; Heim et al., 2008; Heim, Young, Newport, Mletzko, Miller, & Nemeroff, 2009) and reduced hippocampal volume (Buss et al., 2007). Early life adversity also impacts on other key brain regions implicated in stress and depression: reduced medial prefrontal cortical volume in adults having suffered previous emotional abuse (van Harmelen et al., 2010); reduced orbital-frontal cortical volume (Pollak et al., 2010); increased amygdala volume in children who have been institutionalized (Tottenham et al., 2010); and altered cortical affective processing in adults with various psychiatric disorders (Weber et al., 2009). Although the evidence from animal models and human studies that early life stress is a general risk factor which can lead to enhanced stress...
vulnerability and depression is strong, not all those exposed to early life stress develop depression when confronted with stressors as adults (Heim & Binder, 2012). Factors that could account for these differential effects are: sensitive periods of increased brain plasticity throughout development, maturation rates of different brain regions (Tau & Petersen, 2010), puberty (McEwen, 2001) and interactions between individual genotypic variations and early life stress (Heim & Binder, 2012).

The addictive quality of love relationships is not as readily recognized as is the addictive character of dependence upon artificial opiates like heroin and morphine. Love is surely the primal addiction. Panksepp calls it the PANIC/GRIEF instinct. This dual name reflects the fact that the experience of loss (in the context of attachment bonding, which occurs in all mammals) produces a biphasic instinctual response (Panksepp & Solms, 2012).

The despair that can follow the loss of a loved one is all too familiar. Bowlby (1973) considered childhood attachment relationships to be akin to representations of adult romantic relationships and it is thus not surprising that adolescent romantic losses are a significant risk factor for the onset of the first episode of MDD (Monroe, Rohde, Seeley, & Lewinsohn, 1999). Keller, Neale, and Kendler (2007) describe how death of a loved one and romantic breakups are associated with a distinct pattern of depressive symptoms characterised by high levels of sadness, anhedonia, appetite loss, and guilt. Social rejection, more than any other type of stress, can increase the risk for depression (Kendler, Hettema, Butera, Gardner, & Prescott, 2003; Slavich, Thornton, Torres, Monroe, & Gotlib, 2009). Intimate relationships are closely related to the neuromechanisms of depression because of their essential link to stress, cytokine and various changes in neuropeptide systems (Watt & Panksepp, 2009). Social relationships have such a great impact in our lives because they essentially promote survival and a rejection could signal a threat to our self-preservation (Slavich, O’Donovan, Epel, & Kemeny, 2010). Many acts of suicide are attempted following interpersonal loss or
rejections (Richards, 1999). De Rubeis, Lugo, Witthöft, Sütterlin, Pawelzik, and Vögele (2017) found that ‘rejection sensitivity’ was a significant and independent predictor for the worsening of symptoms in men with depressive spectrum disorder. In fact, it seems that a rejection-related stressor is one of the better predictors of MDD (Slavich et al., 2009).

In summary, the second conceptual principle fundamental to this research is that depression is centrally linked to the loss of social attachment figures, social worth and standing, and separation distress, in particular, is critical to the nurturance of social bonds. It should be noted that the activation of separation distress mechanisms does not necessarily occur only in the context of actual separation from attachment figures. The etiological mechanism may also be, for example, an overly sensitive PANIC/GRIEF system, on the basis of genetic factors and/or early developmental separation trauma. We should also recognise that, in humans, with our expansive association cortex, ‘attachment figures’ may be highly abstract and symbolic – one may even become attached to an idea, such as a flag or one’s symbolic position in a social hierarchy (such as the workplace). Surprisingly, the relationship between depressive feelings and the psychology of attachment and loss remains largely unexplored by cognitive neuroscientists. Overcoming this disjunction between brain and mind may therefore go a long way towards integrating the disparate findings from neurobiological and psychological fields (Zellner, Watt, Solms, & Panksepp, 2011).

**Why depression feels bad.** These guiding principles, that is, the subjective experience of the psychological pain of depression and the relationship between depression and social loss, direct the current focus of this research towards the brain systems that generate raw affect, and encourage the problem of “why depression feels bad” (Solms, 2011, p.3) or what Panksepp refers to as the “painfulness” (2010, p. 540) of social loss– a problem which simultaneously contextualizes the conceivable environmental and brain foundations of the condition. From this perspective, depression feels bad because it is underpinned by
affective systems that give rise to specific ‘bad’ feelings, and a thorough articulation of how depression feels bad (sadness, hopelessness, irritability, loss of pleasure or interest), provides meaningful indications as to its specific neuroaffective foundations.

The affective brain systems of PANIC/GRIEF and SEEKING evolved to mediate attachment and loss. When social bonds are broken, the mammal feels a certain kind of psychological pain termed separation distress, the purpose of which is to encourage reattachment with the lost object. If this goal is not achieved, despair soon follows, and it is this despair that most closely resembles depression (Harris, 1989). George Engel’s (1962) clinical observation was that the purpose of ‘giving up’ in despair or the ‘depression-withdrawal reaction’ as he termed it, was to reduce the pain associated with loss and separation. Thus, depression feels bad because (a) it causes psychic pain that promotes reattachments, and (b) it urges us to give up on reunification when such attempts have failed.

This leads us to the central hypothesis under investigation in this thesis: The cornerstone of depression has something to do with unremitting or too easily provoked experiences (real or perceived) of social loss (Solms, 2011) and that the evolutionarily conserved brain mechanisms that regulate the progression from loss to “protest” to “despair” to recovery may underlie the pathophysiology of depression (Solms, 2011; Zellner et al., 2011). In other words, clinical depression may in some way be an aberration of the normal affective response to separation distress. Korf and Bosker’s (2013) perspective is similar to the extent that they too consider depressive mood to be a normal state of the brain but that in MDD, there is an inability to engage in what they refer to as antidepressive transitions. From an affective neuroscience perspective, the subjective experience of depression feels bad because it is intimately linked to the PANIC/GRIEF system; a system that creates social connections and influences adult relationships. When such bonds are broken, the kind of psychological pain which people suffer is akin to grief (Panksepp, 2010). This intense period
of emotional anguish, when unresolved, is followed by psychological and behavioural shutdown, most probably due to an inhibition of global SEEKING activity (Alcaro, Huber, & Panksepp, 2007; Solms, 2011; Watt & Panksepp, 2009; Zellner, et al., 2011). An enhanced intrinsic reactivity of the PANIC/GRIEF system coupled with an intrinsic hypoactivity of SEEKING impulses could promote depression in response to stressors (Panksepp, 2010). At present, this conceptualization of the brain basis of depression most closely aligns with the clinical realities of the condition, and indeed, there is a great deal of neurophysiological data that supports this proposal. In fact, Coenen and colleagues (2012) recently identified an ‘affect-regulating fiber system’ (p. 233) consisting of the medial forebrain bundle (MFB) and anterior thalamic radiation pathways which appear to be the anatomical underpinnings of the SEEKING and PANIC/GRIEF systems.

The affective neuroscience approach. Numerous competing models of human emotion have been developed. The central premise of the affective neuroscience model is that emotions arise from ancient subcortical brain processes, and that many of the more psychologically elaborate emotions experienced by humans arise from the interactions of core emotions with higher brain functions (Panksepp, 1998, 2006). Instinctual behaviours reflect basic affective feelings (Panksepp, 2006). This model considers basic mental processes, brain functions, and emotional behaviours that all mammals share with the purpose of locating the neural mechanisms of emotional expression. A recent meta-analysis of neuroimaging studies by Vytal and Hamann (2010) added support to this approach by concluding that the emotions of happiness, sadness, fear, anger, and disgust were associated with consistent neural correlates.

What is meant by emotion? Panksepp (1998) defines emotions as “psychoneural processes” (p. 48) mediating the behaviour of animals during their interactions with one another and their environment. They are genetically encoded into the subcortical
neurocircuitry of the mammalian brain. They are raw affects that form the bedrock of our mental being and reflect ancient brain/mind processes that are value-laden and shared homologously by all mammals (Panksepp, 2006). These core emotions elicit a particular feeling which guides the encoding of the value of interactions, that is: does the interaction contribute towards survival (positive affects) or hinder survival (negative affects). Although emotions are unconditioned, they are adaptive to experience and promote, via learning, the adoption of strategies (existing or new) that will ensure survival. The brain regulation of emotion is hierarchical. Panksepp (2011) differentiates between: primary processes (instinctual unconditioned stimuli and responses), secondary (conditioned emotional learning and memory), and tertiary (thoughts, reflexive awareness, abstraction) processes, which arise through neocortical interactions with paralimbic and limbic structures (Panksepp & Watt, 2011b). Affects are distinguishable from emotional feelings in that they have an intense developmental influence on the more integrated cognitive mentation of adults. That is, affective experiences at a primary process level influence developments at a secondary and tertiary level (Panksepp & Watt, 2011b). These bottom-up processes have a significant impact on how we feel or think about our experiences. For example, feelings of loneliness and sadness could be cognitively elaborated manifestations of primary separation-distress. Moreover, affects start out without any particular connection to things in the environment; it is through experiential maturation that we become invested in objects in the world. Failing to achieve or sustain relationships with our desired objects causes us psychological pain which can, in some individuals, be the catalyst for the onset of depression. Human emotions are so varied and complicated that in order to gain a better understanding, we are compelled to go back to basics, that is, to the basics of emotion.

**Why the affective neuroscience model in particular?** Since a major aim of affective neuroscience is to delineate primary-process consciousness into its various networks and
related functions, with a special focus on emotional feelings (Panksepp, 2004), it is a uniquely appropriate conceptual framework for studying the brain basis of depression. Psychiatric disorders cannot be fully understood without a fundamental grasp of the neurobiological essence of core affects, since neurochemical changes within these primordial emotion systems lead to changes in affect that are of psychological significance. The empirical value of this approach rests on two fundamental assumptions; firstly, emotions have been evolutionary preserved to do something specific in relation to biologically important and life-threatening events, and secondly, these emotions are felt as specific positive or negative feelings for the purpose of promoting behaviours that encourage survival and avoid destruction (Panksepp, 2005a; Zellner et al., 2011). The model is framed within a dual-aspect monism philosophy: core emotional behaviours and their subjective affects originate from the same subcortical neural dynamics (Panksepp, 2011). Unlike other models of emotion that focus either on purely top-down mental processes (psychoanalytically based) or on reductionist biological principles (psychiatrically based), the affective neuroscience model adopts a neuropsychological perspective, studying the mind and brain, where brain and mind are conceptualized as two different aspects of the same ‘thing’ (Solms & Turnbull, 2002). In this regard, Hofer (2005) argues that evolutionary principles provide a common theoretical basis that can be shared by both neuroscientists and psychoanalysts. Affects are further distinguishable from emotional feelings in that the origin of regulation of affective consciousness is subcortical, whereas that of cognitive consciousness is neocortical. The neocortex is not implicated in the experience of core affects. Such a distinction allows for the integrated study of psychiatric illnesses from a joint neurobiological and psychological perspective, whilst recognising the complex interaction of affects and cognitions in adult psychology (Panksepp, 2006).
The affective neuroscience model stands apart from other models of emotion in that this approach relies on preclinical evidence to identify basic emotional networks in mammalian brains; affective mechanisms that are homologously identifiable in humans. Animal models lend themselves to levels of neuropsychological investigation that are more exact than the levels of analyses that can be achieved by human or brain imaging studies (Panksepp, 2014a). There is substantial cross-species evidence to support Panksepp’s claim that many affects arise from subcortical brain functions shared by all mammals (Alcaro, Panksepp, Witczak, Hayes, & Northoff, 2010; Damasio et al., 2000; Mobbs et al., 2007). For example, Buhle et al. (2013), using fMRI with normal participants, confirmed that the periaqueductal gray (PAG) plays an important role in human negative affect, supporting previous evidence from research in animals (Panksepp, 1998). However, this approach is not uncontested. Blumberg and Sokoloff (2001) argue that the use of ‘anthropomorphic’ reasoning in animal research is inappropriate. But there is categorical behavioural data for animal emotions; from Darwin (1872) who claimed that the difference between humans and other animals is one of degree and not of kind, to more recent research by Mendl, Burman, and Paul (2010), who showed that dogs who exhibited separation-type behaviour were also likely to be experiencing a negative affective state. More importantly, this model allows for predictions to be made about affective changes in humans following manipulations similar to those undertaken in animal research, since the tertiary processes that arise from separation distress in humans, such as shame or guilt, are founded on the more rudimentary processes of subcortical brain regions shared by all mammals (Panksepp, 2005b).

**Core emotion systems.** Panksepp has identified seven primary-process emotion systems, namely: SEEKING, LUST, CARE, and PLAY (emotionally rewarding states) and FEAR, RAGE, and PANIC/GRIEF (emotionally punishing states), that can be elicited through activation of subcortical networks (Panksepp, 2014b).
The core emotion systems of depression. The separation-distress hypothesis of depression allocates a role to two, closely interactive, systems in the genesis of depression: SEEKING and PANIC/GRIEF.

The SEEKING system is a positively motivated action system that when activated, encourages the organism to engage with the real world in order to satisfy its needs; it is a “foraging/exploration/investigation/curiosity/interest” system (Panksepp, 1998, p.145). Optimal functioning of this system leads to positive feelings of engagement, anticipation and excitement which mediate reward-learning. The mesolimbic dopamine (ML-DA) system is the principal neurochemical involved in the SEEKING system (Alcaro & Panksepp, 2011). DA is the main catecholamine in the mammalian brain and is implicated in inter alia: cognition (Nieoullon, 2002); emotional memory (Labar & Cabeza, 2006; Richardson, Strange, & Dolan, 2004); positive reinforcement (Tripp & Wickens, 2012); reward (Zweifel et al., 2009); fear (Carvalho, De Oliveira, Da Silva, & Brandao, 2009); regulation of locomotor activity (Medvedev et al., 2013); anxiety (Zarrindast & Khakpai, 2015); learning and choice incentives (Collins & Frank, 2014), behavioural arousal (Taylor et al., 2016) and depression (Lemke et al., 2006; Porcelli, Drago, Fabbri, & Serretti, 2011). Animal research has shown that a deficit in DA transmission in the ML pathway can lead to both helplessness and anhedonia (Nestler & Carlezon, 2006) and down-regulation of the SEEKING system leads to feelings of disinterest, apathy and hopelessness (Zellner et al., 2011). The ‘dopamine pleasure hypothesis’, originally proposed by Wise (1980), stipulated that DA was a mechanism for pleasure. More recently, however, and with particular reference to anhedonia, this view has been challenged in light of increasing evidence that loss of DA does not necessarily result in a loss of pleasure. In this regard, Berridge & Kringelbach (2015), argue that anhedonia should be interpreted not as ‘loss of pleasure’ but rather as a deficit in incentive motivation and that the role of DA in pleasure relates more specifically to ‘wanting’
(mediated primarily by the NAc core) than ‘liking’ (mediated primarily by processes in the NAc shell; Saddoris, Cacciapaglia, Wightman, & Carelli, 2015).

The ML-DA system is also often referred to as the “reward system”. But this is an overgeneralisation as mesolimbic DA also plays a role in aversive motivation (e.g. social defeat; Salamone & Correa, 2012). Furthermore, the word ‘reward’ is often used to refer to different things such as pleasure, learning, motivation or emotion. However, there are distinct aspects of motivation that are differentially influenced by DA. For example, accumbens DA does not mediate appetite (Smith, Berridge, & Aldridge, 2011), but is involved in appetitive and aversive motivational processes such as behavioural activation (Lex & Hauber, 2010), exertion of effort (Mai, Sommer, & Hauber, 2012) and approach behaviour (Nicola, 2010). Of particular significance in the context of this piece of research is that DA’s prominent role in reward is that it activates approach. Thus, it is important here to emphasise that it is the “euphoria of appetitive eagerness”, not the “pleasure of sensation”, that drives the SEEKING system (Alcaro & Panksepp, 2011, p.1807).

Other neurochemicals, in addition to DA, are also implicated in reward (for example, GABAergic and glutamatergic mechanisms). For instance, opiates are self-administered into the lateral hypothalamic area and PAG, indicating that there are additional trigger zones for reward (Ikemoto, 2010). Although typically, substances of abuse exert their influence by increasing DA in the NAc, there is increasing evidence that endogenous opioids are also implicated in the rewarding effects of substances of abuse (Colasanti et al., 2012). To illustrate, the opioid receptor antagonist naltrexone has been used successfully for the treatment of alcoholism, as alcohol increases DA via its effects on opioids and GABA (Volkow, 2010). Furthermore, MOR availability has been found to be increased in the limbic brain regions of cocaine users (Ghitza et al., 2010). This interaction also effects the regulation of mood and motivation.
PANIC/GRIEF is a ‘bidimensional’ system that regulates social affect. It generates painful feelings associated with social loss and gratifying feelings associated with social inclusion. Interestingly, often the terms we use to describe the pain of a physical injury are also used to describe the pain we feel following a romantic breakup or some sort of social rejection. There is accumulating research to show that this might not be mere coincidence. Social and physical pain share overlapping neuroanatomy and some neurotransmitter substrates (Way, Taylor, & Eisenberger, 2009). The unpleasantness of physical pain is associated with various parts of the anterior cingulate cortex (ACC) and anterior insula (Peyron, Laurent, & Garcia-Larrea, 2000). These same parts of the ACC and anterior insula are also associated with social pain (Hadland, Rushworth, Gaffan, & Passingham, 2003). Eisenberger, Taylor, Gable, Hilmert, and Lieberman (2007) demonstrated how people who had close and socially supportive daily interactions exhibited less activity in the dorsal ACC and Brodmann's area. The importance of the ACC in mood regulation is widely reported. Mayberg et al. (2005) has shown that deep brain stimulation (DBS) of the white matter just beneath the ACC has significant antidepressant effects in refractory MDD. Better responses to cognitive behavioural therapy have been linked to ACC volume and functional connectivity with the fronto-parietal cortex in subjects with MDD (Sambataro et al., 2018). Dewall et al. (2010) demonstrated how acetaminophen (a physical pain reliever) lessened hurt feelings by reducing activity in brain regions involved in social pain processes (that is, the dorsal anterior cingulate cortex and anterior insula), confirming the overlap between the social and physical responses to pain.

Along similar lines, we often use terms such as ‘warm and fuzzy’ and ‘heart-warming’ to refer to intimate experiences and this too is more than mere coincidence. Social and physical warmth may be closely related based on some shared neurocircuitry (Panksepp, 1998). It is known that opioids mediate changes in body temperature (Adler, Geller, Rosow,
& Cochin, 1988). It has been shown that in humans, morphine can reduce the unpleasantness of noxious thermal stimuli and is implicated in the subjective experience of warmth (Morin, Duncan, Lavigne, Boily, & Bushnell, 1999). Imaging studies have shown that there is an overlap between neural activity during social and physical warmth in opioid-dense regions such as the insula and ventral striatum (VS; Inagaki & Eisenberger, 2013). More recently, Inagaki, Irwin, and Eisenberger, (2015) provided additional support that social and physical warmth share opioid dependent mechanisms, by demonstrating that naltrexone could reduce feelings of social connection in relation to a warm object but not to a cold object. Moreover, opioidergic blockade by naltrexone (an opioid antagonist) can reduce affiliative feelings such as cosy, comforting and secure (Schweiger, Stemmler, Burgdorf, & Wacker, 2014).

At a neurochemical level, there is considerable preclinical evidence that opioids feature prominently in mediating social bonds. Separation distress circuits are closely linked to opioid-sensitive pain regulation (Panksepp, 2005a) since MOR agonists such as morphine have been shown to reduce separation-distress crying, while blocking the receptors with an opioid antagonist can induce separation distress behaviours in various animal infants (Nelson & Panksepp, 1998; Panksepp, 2004; Panksepp, Herman, Vilberg, Bishop, & De Eskinazi, 1980). In various non-human primate studies, it has been demonstrated how exogenous opiates can act as a substitute for social contact and how blocking the MOR system encourages social interaction (Graves, Wallen, & Maestripieri, 2002; Martel, Nevison, Simpson, & Keverne, 1993). Even prosocial activities like play and grooming are associated with µ-opioid release (Loseth, Ellingsen, & Leknes, 2014). Likewise, in humans, social rejection activates the endogenous opioid system (Eisenberger, 2012b) and disruption of the MOR system affects the ability to form social bonds (Loseth et al., 2014). The role for MOR in response to negative affects related to social loss (Zubieta et al., 2003) and in social bonding and reward (Tops, Koole, Ijzerman, & Buisman-Pijlman, 2014) are evident. MOR
enhancement increases the seeking of high-value rewards (Taha, 2010) and is also implicated in sexual preference. In a recent study using male participants, Chelnokova et al. (2014) showed that facial attractiveness was increased by morphine and decreased by naltrexone. Reductions in \( \mu \)-opioid neurotransmission in the rostral anterior cingulate have been shown to correlate with experimentally induced sadness states (Zubieta et al., 2003) and hypermetabolism in the same area is associated with a poor response to antidepressants in patients with unipolar depression (Mayberg et al., 1997). Separate MOR mechanisms mediate positive (social acceptance) and negative (social rejection) affects (Hsu et al., 2013). Thus, the pleasant feelings of social contact (such as contentment and well-being) are induced by endogenous opioid release, while the unpleasant feelings, like separation distress, are associated with social isolation and are induced by opioid withdrawal (Panksepp, Herman, Conner, Bishop, & Scott, 1978b; Panksepp, Nelson, & Bekkedal, 1997). It is important to note that the different chemistries involved in mediating social interactions are very complex. Other than \( \mu \)-opioid s, \( \kappa \)-opioids, \( \delta \)-opioids, oxytocin, DA and serotonin are also involved. For instance, there is evidence that points to the possible involvement of the DA system in human mothering. fMRI studies have shown that the brain activity of mothers exposed to infant stimuli, coincide with regions of the mesocorticolimbic DA system (Barrett & Fleming, 2011). Mileva-Seitz et al. (2012) found an association between genetic variation in two DA receptor DRD1 and DRD2 and maternal responsiveness. Furthermore, MOR mechanisms interact with the DA system in reward processing (Colasanti et al., 2012) and with oxytocin and DA in social bonding (Tops et al., 2014).

To summarise, the PANIC/GRIEF and SEEKING symptoms interact in the separation-distress hypothesis of depression in the following way: (a) sustained overactivity of the PANIC/GRIEF system (the protest phase, also known as separation distress) can, if prolonged, lead to a downward cascade of depressive affects or hopelessness; (b) the despair
phase that follows (and shuts down) protest, due mostly to underactivity of the SEEKING system, can lead to the chronic anhedonic states typical of depression; (c) the protest phase is associated with aroused DA-mediated SEEKING urges (i.e. attempts at reunion) and (d) kappa opioids partly mediate despair by shutting down SEEKING through their effect on ventral tegmental area (VTA) output. The sequence just described occurs in the context of normal bereavement (where the loss, despite protest, is not followed by a reunion) and depression is the pathological (excessive or maladaptive) engagement of this mechanism (Panksepp & Watt, 2011a; Panksepp, Solms, Schläpfer, & Coenen, 2014; Zellner et al., 2011). The shutting down of protest by prolonged kappa opioid receptor signalling, is also coupled to sustained stress cascades (Knoll & Carlezon, 2010). These processes have a de-energizing effect on the SEEKING system. Essentially, in this condition, the organism is unmotivated, anergic and unable to experience pleasure -- feelings characteristic of depression.

The purpose of this shutdown mechanism is survival: the termination of separation-distress vocalizations has been theorised to protect against predators, to ensure the juvenile does not wander too far from home-base and to preserve metabolic resources. There is an adaptive risk to remaining attached to an absent caregiver and hence the despair phase evolved to shut down the attachment seeking behaviours of protest (Freed, 2009). Shutdown mechanisms that are used in early separation-distress situations can be re-engaged by adults in response to social losses experienced later in life. Normally, these shutdown mechanisms are self-limiting, but in depression, it seems that the adaptive purpose of such mechanisms goes awry (Watt & Panksepp, 2009). People who are unable to “self-limit” are more prone to depression. The despair persists in these cases, leading to a stress cascade that becomes metabolically over-demanding (HPA axis activation; CRF effects; reduction of oxytocin and opioids; cholecystokinin, and dynorphin effects; hypoactivity in brain areas involved in
executive functioning; increased processing in limbic and paralimbic regions; BDNF decreases and hippocampal atrophy), along with the accompanying and inescapable symptoms of depressed affect. This leaves unanswered the question as to how some people are able to make a healthy recovery from mourning a loss, while others are unable to “self-limit” and remain chronically depressed. Zellner et al. (2011) argues that part of the answer relates to the extent to which a recent loss evokes feelings that relate to unresolved early losses. Certain types of losses, such as a child losing a mother or loss of a beloved partner, can be particularly painful leaving some people feeling especially vulnerable and exposed. The separation distress in these instances is often penetrating, and acceptance of the loss very hard to achieve. Another factor to consider is that of emotional resilience. Some individuals are more vulnerable to stress and cannot cope with even minor losses. They are more sensitive to the psychological pain of separation distress, possibly because of genetic susceptibility (Barr et al., 2008).

**DSM revisited.** Before proceeding with a more detailed discussion of the PANIC/GRIEF and SEEKING systems, it is worth revisiting the DSM-5 classification of depression in light of the separation-distress hypothesis. Sadness and hopelessness are commonplace feelings that depressed patients use to describe their mood. Yet these symptoms are not adequately addressed in the current DSM-5 classification of depression and require further elaboration as they relate particularly to the separation-distress model of depression adopted here. Specifically, there are patients who report feeling depressed and sad, pointing to the fact that depression often comes after a loss of some kind. Some depressed patients on the other hand, do not report any feelings of sadness, supporting one of the central themes of the separation-distress hypothesis of depression, namely, that sadness is extinguished by worsening depression. Hopelessness, likewise, is closely related to depression. The feeling of not being able to go on, of ‘giving-up’ on the daily struggle, also
lends support to the separation-distress hypothesis in that depression must have some kind of constraining effect on motivational arousal systems, that is, the SEEKING system. Furthermore, a core criterion in the DSM-5 for MDD is loss of interest, specifically “markedly diminished interest or pleasure in all, or almost all, activities” (APA, 2013, p. 160). Taking interest in the world and the rewards it has to offer is essentially linked to the operations of the SEEKING system (Watt & Panksepp, 2009).

**The PANIC/GRIEF system, the social bond and protest.** Because of the fundamental survival value of social attachments, especially the bond between infant and mother, it is likely that the PANIC/GRIEF system was strongly selected for early on in mammalian evolutionary history, and possibly intensified in the hominoid brain (Watt & Panksepp, 2009). To this end, the exceptional regulatory capacities of these systems, quite conceivably an evolved extension of more basic homeostatic processes (Nelson & Panksepp, 1998), far exceed simple conceptualisations of separation distress and attachment as being akin to operant functioning (Freed, 2009). Rather, they are an essential form of behaviour motivated by its own internal dynamics (Panksepp, 1998). Harry Harlow’s seminal observations on infant monkeys demonstrated that maternal bonding arises independently from the rewarding properties of other biological necessities such as food (Harlow & Zimmerman, 1959). These findings have been replicated in humans and other species and it is now well established that youngsters fail to thrive in socially impoverished environments (Panksepp, 1998). The central function of the PANIC/GRIEF system appears to be the close monitoring of social proximity, such that if separation occurs from an attachment figure, activity in this system encourages the seeking of reunion (Nelson & Panksepp, 1998). Activation of this system therefore requires that an attachment does indeed exist. Two key processes underlie this capacity: firstly, that attachment promotes a sense of security and
comfort, and secondly, that when broken, induces a particular kind of psychological pain and
behavioural arousal, namely separation distress.

The concept of attachment is well established in scientific literature, and is generally
defined as a selective emotional or social bond, which appears to function as a ‘secure base’
for interaction with the environment (Ainsworth, 1989) and group cohesion (Smith, Murphy,
& Coats, 1999). While social bonds are not always easily measured, a number of
physiological correlates and behaviours index the existence of a secure attachment. Close
physical contact is the hallmark of an attachment; for example, young rat pups will
preferentially huddle around their mother (Kojima & Alberts, 2011) and bonded prairie voles
share nests and remain side by side until death (Wang & Aragona, 2004). Allogrooming is
another common behavioural display of social bonding (Saltzman & Maestripieri, 2011),
involving the cleaning and maintenance of another individuals’ bodily surface as is
commonly observed in primates (Dunbar, 2010). Visual tracking of the attached figure has
also been used to index close affiliation (Kraemer, 1992). In humans, the ‘strange situation’
test, first introduced by Ainsworth (1989), in which a young child’s response to an unfamiliar
situation is assessed, has become a landmark in human attachment research and is thought to
reveal attachment styles with primary caregivers. However, across the field, reactions to
separation, commonly referred to as ‘protest’ behaviours, constitute the core criterion against
which an attachment is judged (Carter, 1998; Panksepp, 1998).

During the acute protest phase, an infant will typically emit distress vocalizations and
begin to search for its lost caregiver. In young mice, these ultrasonic calls tend to range in
frequencies between 70 and 80 kHz and were described as ‘whistles of loneliness’ when they
were first discovered in 1956 by Zippelius and Schleidt (1956). At this point already, these
calls were understood to reflect both an adverse affective state and an attempt by the pup to
commutate this distress to the mother. Indeed, caregivers of many different species readily
respond to these sounds (Bos, Hermans, Montoya, Ramsey, & van Honk, 2010; Nelson & Panksepp, 1998) and they have been clearly dissociated from other kinds of distress vocalizations (Panksepp, 1998). “Crying is the human homologue of the separation call” (Bos et al., 2010, p.114) and subserves a similar role in mother-infant bonding (Christensson, Cabrera, Christensson, Uvnas–Moberg, & Winberg, 1995). Infant separation calls seem to be mediated by neural systems similar to those that mediate anxiety in adult animals and humans (Hofer, 2005). In humans, however, real protest only occurs once the motor systems are developed and prior to this, crying behaviour is soothed by non-specific caregivers (Panksepp, 1998). Once the child reaches approximately six months, stable attachments begin to develop. The disappearance of the attached figure usually precipitates this distress response, and in rats is amplified if the pup is in unfamiliar surroundings (Pettijohn, 1979). Physical contact is not typically necessary at all times, but in the form of touch, it has been shown to be particularly effective in soothing distressed animals (Bermant, 1963) even though the relative proximity of the mother is enough in most cases for inhibiting PANIC.

The affective valence of the PANIC/GRIEF system is experienced as psychological suffering, not simply as a metaphorical expression. This is because it appears to have evolved in part from brain mechanisms that mediate the perception of physical pain (Panksepp, 1998, 2005a). From an evolutionary perspective, this is a reasonable proposition as humans are born entirely reliant on caregivers to provide for all basic needs, thus a painful symptom indicating that the caregiver bond is under threat, would essentially promote survival. Recent evidence from neuroimaging studies confirms this suggestion (Eisenberger, Lieberman, & Williams, 2003; Eisenberger, 2012a). It is known that social rejection and physical pain share common neuronal pathways (Kross, Berman, Mischel, Smith, & Wager, 2011), but it was the observation of the striking parallels between opiate addiction and social dependence that initially informed this impression (Panksepp et al., 1978b) in that the molecules which are
effective in alleviating physical pain are intimately tied to those that mediate psychological pain (Panksepp, 2010).

Bereavement in adult humans provides an important window into the subjective reality of this kind of psychological pain, one that is very similar to protest behaviours described in the animal literature. In their comprehensive account of the processes of bereavement, Stroebe and Stroebe (1987) write:

The initial numbness gives way to a period of strong emotions, with extreme psychological distress and physiological arousal as awareness of the loss develops. This is accompanied by intense yearning for the lost person, with pangs of deep pining, and spasms of uncontrollable sobbing. At this stage there is often an overriding urge to search for the deceased…The bereaved moves restlessly around the environment, searching, and is intensely, almost obsessively preoccupied with memories, thoughts and possessions of the deceased. Eventually …searching for the lost person is abandoned …the bereaved person despairs that anything worthwhile in life can be salvaged, and apathy and depression set in. (p.14)

References here to ‘deep pining’, ‘uncontrollable sobbing’, ‘obsessive searching’ and ‘despair’, establish important congruencies with animal models of separation distress. Terms like ‘agitated searching’, calling and ‘deep depression’ are commonly used to describe separation distress in infant animals (Kaufman & Rosenblum, 1967). Moreover, somatic distress, including sighing, respiration and a loss of strength, have also been described in the acute stages of loss (Lindemann, 1944), and are indicative of the systems-level dysregulation (panicked state) induced by the PANIC/GRIEF system. Subjective reactions to loss have been described as ‘painful’ (Bonanno & Kaltman, 2001), ‘shocking’ and ‘deeply saddening’ (Anderson & Dimond, 1995), always imbued with a deep sense of loneliness. While human research into the ancient sources of core affect are always confounded to some extent by
cognitive ruminations, the cross-species parallels in reactions to loss strongly indicate subcortical brain foundations of this affective state. We assign an intrinsic value to our own emotional experiences—they are felt to be positive or negative, rewarding or punishing, pleasant or unpleasant, and so forth. Likewise, there is considerable research into the affective states of animals, showing that animals too can suffer or experience pleasure (Boissy et al., 2007; Mendl, 2001; Mendl & Paul, 2004; Mendl, Burman, Parker, & Paul, 2009). Moreover, there is conclusive evidence for the existence of experimentally evoked subcortical reward and punishment functions, providing substantial support for the idea that raw affective feelings are a product of ancient subcortical midline brain networks, and that these states also feel good or bad to animals. It is from these same brain areas that self-reports of particular affective experiences in humans can be elicited, and the descriptions of these feelings are analogous to the emotional behavioural patterns elicited in animals (Panksepp, 2011). Subcortical stimulations (EBS) can elicit meaningful emotional behaviours in animals (emotional vocalizations) and humans alike (Panksepp, 1985). To illustrate, the PANIC/GRIEF system is highlighted by the density of glutamate, CRF and endorphin receptors that run between the midbrain PAG and dorsomedial thalamus, down to the ventral septal area, preoptic areas and bed nucleus of the stria terminalis, and in higher species, the anterior cingulate (Panksepp, 1998). Localized electrical stimulation of these brain regions has yielded similar findings in a variety of animals ranging from dogs and Guinea pigs to chickens (Panksepp, Herman, Vilberg, Bishop, & De Eskinazi, 1980). In humans, DBS of the anterior mid-cingulate cortex (aMCC) yielded feelings of anticipation of a challenge coupled with strong motivation to “overcome it” or as the authors described it, the “will to persevere” (Parvizi, Rangarajan, Shirer, Desai, & Greicius, 2013, p.1362). Feelings of apathy have been reported following DBS of the subthalamic nucleus (STN) in Parkinson's patients (Ricciardi et al., 2014). Furthermore, DBS studies also report that the ventral part of the STN is
 implicated in the emotional valence of stimuli that is, in the representation of the affective value of the environment, and that DA enhances the processing of pleasant information (Buot et al., 2013). With regards to depression, DBS of the subgenual cingulate white matter have resulted in significant improvements of symptoms (Johansen-Berg et al., 2008; Mayberg et al., 2005). Coenen et al. (2011) reported similar improvements in depressed patients with DBS of the medial forebrain bundle.

Panksepp and Watt (2011a) argue that it is sudden opioid cessation that contributes to the negative feelings in animals and humans that ensue after separation from attachment figures. For example, Naloxone, an opioid antagonist, increases distress vocalizations, which are effectively attenuated by morphine, even at extremely low doses (Herman & Panksepp, 1978, 1981). The modulating effects of opioids operate primarily through µ-receptors, which are involved in reward processing (le Merre, Becker, Befort, & Kieffer, 2009); hedonic mediation (Smith & Berridge, 2007); positive affect (Negus et al., 1993), negative affect states (Kennedy, Koepp, Young, & Zubieta, 2006), stress-associated behaviour (Bali, Randhawa, & Jaggi, 2015), memory (Iordanova, McNally, & Westbrook, 2006), and decision-making (Laurent, Morse, & Balleine, 2015). The intrinsic rewarding effects of µ-opioids have been demonstrated through the use of place preference and stimulation paradigms (Negus et al., 1993; Olmstead & Franklin, 1997). Opioids appear to exert their remarkable appeasing effects by re-establishing an affective state of social connectedness, to the extent that animals without this system are numb to the rewarding effects of maternal comfort (Moles, Kieffer, & D'Amato, 2004). Animals experiencing low opioid activity will actively seek out social connection (Nelson & Panksepp, 1998). Rodents kept in isolation consume more morphine compared to situations where social interaction is allowed (Consorti, Castellano, Oliverio, & Pavone, 1992). Social play in rats is heightened by low-dose morphine treatment (Trezza & Vanderschuren, 2008). Increased levels of social
approach exhibited by rats experiencing periods of prolonged social isolation can be curbed by morphine (Hol, Ruven, Van Ree, & Spruijt, 1996). Taken together, these studies confirm that opioid-mediated circuits and social interaction are closely related and that the rewarding properties of morphine can be altered by changes in the social environment and that manipulating endogenous opioid systems in turns affects social interactions.

To a lesser extent, prolactin, oxytocin and cholecystokinin have also been found to relieve separation distress (Panksepp, 1998; Weller & Feldman, 2003) but the major tranquilizers, which may at face value seem like an obvious candidate, have minimal effect (Panksepp, 1998). Neuroimaging studies in humans have now begun to contribute to the cross-species relevance of this body of literature, with evidence coming from positron emission tomography (PET) studies in which feelings of sadness, a variant of the social pain elicited by social isolation, have been associated with low opioid activity in the brain (Zubieta, Dannals, & Frost, 2003). Hsu et al. (2013, 2015) used positron emission tomography (PET) to demonstrate that µ-opioid receptor activation is ‘protective’ and implicated in reducing social distress and mediating social reward in human subjects. They showed that despite the negative affect of rejection, only healthy controls exhibited MOR activation whereas the depressed patients exhibited MOR deactivation and slower recovery from rejection, confirming that altered endogenous opioid activity is implicated in impaired emotion regulation. Yovell et al. (2016) showed that Buprenorphine, a partial µ-opioid agonist and kappa antagonist, significantly decreased suicidal ideation in severely suicidal patients. Furthermore, they made the tentative inference that ultra-low-dose Buprenorphine could be more effective in ameliorating feelings related to rejection and abandonment and less effective in addressing the symptoms of anhedonia. In terms of Panksepp’s theory, this translates to “attenuation of the hyperactivation of the endorphinergic PANIC/GRIEF system, without reversing the partial shutdown of the aminergic SEEKING system” (p.6). Lending
support to Yovell’s view, Bershad, Seiden, and de Wit (2016) demonstrated how
Buprenorphine was linked to decreases in perceived social rejection, independent of any
subjective feelings of euphoria.

Of the key activators of PANIC episodes, glutamate and CRF appear to play a
primary role (Panksepp, 1998). Studies have demonstrated that activating receptors for
glutamate and CRF can elicit distress vocalizations (Panksepp, Solms, Schläpfer, & Coenen,
2014). Hormones secreted by the HPA response, particularly cortisol, both initiate, and are
released following separation and decline considerably upon reunion with the attached figure
(Hennessy, 1997; Levine, 1994; Reite & Boccia, 1994). It has been shown that μ-opioid
agonists reduce cortisol concentrations and stimulate prolactin and growth hormone (Hoehe,
Duka, & Doenicke, 1988). Other physiological outcomes of the separation distress response
include cardiac acceleration, alterations in temperature and sleep, generalized brain and
behavioural arousal as well reductions in growth hormones (Hennessy, Deak, Schiml-Webb,
Carlisle, & O’Brien, 2010; Hofer 2005), many of which are observed in human bereavement
(Hofer, 1984), and which are argued to pose an increased risk of metabolic exhaustion for the
distressed individual (Watt & Panksepp, 2009). To this end, when the biologically optimal
outcome of reunion with the attached figure fails to occur, protest dissolves into a state of
despair, signaling that the infant has ‘given up’ their pursuit.

The despair phase, SEEKING system and depression. As previously mentioned,
Bowlby (1973) noticed that an initial phase of separation anxiety was followed by an acute
decline in behavioural responsiveness in maternally deprived infants. The process through
which this termination of protest occurs appears to facilitate a withdrawal from all pursuits of
normal rewards (Zellner et al., 2011). Tsiouris (2005) describes a kind of metabolic
depression, marked by lethargy and negative affective tone, which is akin to a state of
hibernation, and which underlies the vegetative symptoms of major depression. For instance,
during this second phase of social loss (despair), infant pig-tailed or rhesus macaques will sit hunched, cradling their bodies with their heads held low, droop the corners of their mouths and refrain from all play activities with the rest of the group (Keedwell, 2008). Similarly, young Guinea pigs submitted to extended isolation retreat into a passive, crouched stance, with their eyes closed and their hair on end (Hennessy et al., 2004). Maternal figures separated from their young also present with despair. Mother rats exhibit reduced mobility, indicative of poor coping, which subsequently impairs their normal maternal functioning (Boccia et al., 2007).

The brain mechanisms of this shutdown process are less well known than those of active separation distress, but the sequel of neurophysiological events that characterise protest are acknowledged as the establishing factors in the subsequent development of despair (Hennessy, 1997), and which are now widely implicated in the genesis of depression. Of these factors, the activation of the HPA axis and the release of corticosteroids figures prominently (Hennessy, 1997), establishing social loss as a robust and indisputable psychogenic stressor. Cascade effects include the increased production of proinflammatory cytokines and lymphocyte proliferation suppression, both of which are associated with ‘sickness behaviours’ in which animals display increased sleepiness and reductions in exploration and social or sexual activity (Hennessy, Kristopher, Caraway, Schiml, & Deak, 2011). Two major neuropeptides, CRF and dynorphin, mediate exposure to stress (Nestler & Carlezon, 2006) in the following way: stress increases the release of CRF; CRF activation induces dynorphin release; dynorphin selectively activates κ-opioid receptor (KOR); KOR activation induces a negative affective state (Bali et al., 2015; Land et al., 2008; Van’t Veer & Carlezon, 2013; Van’t Veer et al., 2013). The pathway via which stress exerts its effect on dynorphin production appear to be stress-induced cAMP response element binding protein (CREB) activation (Bruchas, Land, & Chavkin, 2010; Nestler & Carlezon, 2006) and the
release of DA (Preusner, Champagne, Meaney, & Dagher, 2004), perhaps via glutamate receptor stimulation (Suaud-Chagny, Chergui, Chouvet, & Gonon, 1992). Dynorphin is released in the striatum and NAc in response to DA activation of the D1 D2 DA receptor (Shippenberg, Zapata, & Chefer, 2007; Walker & Koob, 2008). This effect is sustained for some time following the cessation of stimulation, indicating that it may be a compensatory response to elevations in extracellular DA levels and may play an important role in counteracting the inflammatory effects of DA in these regions (Wang et al., 2012). Ultimately however, overproduction of dynorphin sustains a feedback loop to decrease DA transmission by inhibiting medial forebrain DA (Di Chiara & Imperato, 1988) and increasing DA transporter (DAT; Thompson et al., 2000), which is thought to account for the dysphoric effects of dynorphin, and which characterizes the despair phase.

How precisely KOR systems influence mood is not yet fully understood but the prevailing opinion is that their effects are influenced by the mesolimbic DA reward circuit and KORs within this circuit directly regulate DA function and behaviour (Donahue et al., 2015). KOR activation in the serotonergic neurons of dorsal raphe nucleus (DRN), the dopaminergic neurons of the VTA, and neurons of the NAc are all implicated in the stress response (Bruchas et al., 2010; Van't Veer & Carlezon, 2013), suggesting that dynorphin regulates mood by controlling serotonergic and dopaminergic inputs to the NAc, but these circuit mechanisms are not yet clear (Ehrich et al., 2015b). It is known that KOR agonists can induce dysphoria and anxiety in humans (Taylor & Manzella, 2016; Vortherms & Roth, 2006) and that drugs with KOR antagonist activity have been shown to produce antidepressant activity in patients with MDD (Ehrich et al., 2015a). The relationship between dynorphin and dysphoria in animal models is likewise well documented. Repeated immobilization stress reduces motivational behaviour and correlates with dynorphin/κ-opioid changes (Lucas et al., 2011); there are increases in dynorphin A and B in the hippocampus.
and NAc during learned helplessness (Shirayama et al., 2004); prolonged stress can produce learned helplessness and dysphoria, which is attributable to an increase in dynorphin in the striatal region (Lucas, Dragisic, Duwaerts, Swiatkowski, & Suzuki, 2011) and lastly activation of dynorphin/κ-opioid receptor system leads to prolonged stress-induced depression-like behaviour in rodents (Land et al., 2008). It is also known that KOR agonists induce inhibition of DA signaling in the NAc in animal models. The infusion of KOR agonists into the NAc results in anhedonic and dysphoric behaviours in animal models (Muschamp et al., 2011), meaning that alterations in the expression of KORs in the NAc could possibly lead to long term changes in the function of the mesolimbic system. Studies have shown that without KOR, as seen in knockout mice, these animals function in a ‘sensitized state’ in which the behavioural effects of psychostimulants are ineffective in altering behaviour demonstrating that dynorphin is critical in regulating the reward functions of the DA system (Chefer et al., 2005). What these various studies appear to suggest is that the effects are causal, that is, the aversive effects of KOR agonists are mediated by inhibition of NAc DA signaling. In relation to depression then, the down-regulation of the mesolimbic DA system may be linked to increased dynorphin signaling. This dynorphin-driven shutdown of SEEKING systems (i.e. ‘giving up’ in despair) may represent a subset of cases where loss of motivation is the most prominent feature (Zellner et al., 2011). Recently though, Ehrich et al. (2015b) demonstrated that the aversive effects of κ receptor activation required arrestin-dependent p38α MAPK activation in DA neurons but did not require inhibition of DA release in the NAc, which is contrary to the prevailing view that inhibition of mesolimbic DA release mediates the aversive effects of KOR activation. Although they confirmed that KOR activation does inhibit DA release in the NAc, they argued that KOR activation had other actions in the VTA-reward circuit and that aversion was not the result of a simple reduction in DA transmission. They further hypothesised that KOR activation in
different circuits could mediate different types of aversion, such as anhedonia, depression, dysphoria, or anxiety.

The most marked feature of despair is a generalized behavioural and psychic lethargy, in which motivated engagement with the environment and the ability to actively cope is diminished. First discovered in 1954, Olds and Milner noticed that electrical stimulation to key brain regions, namely the lateral hypothalamic-medial forebrain trajectory, resulted in a ‘reward phenomenon’ for which rats would repeatedly self-stimulate. Later on, Glickman and Schiff (1967) observed that stimulation of this same area produced species-typical engagement with the environment and it has subsequently been referred to as “the brain reward system” (Moriyama, Ichimaru, & Gomita, 1984), the “behavioural activation system” (Gray, 1985), and the “reward system” (Koob, 2009) in recognition of its role in learning and appetitive motivation.

Conceptualised more recently as the SEEKING urge, Panksepp (1998) has brought attention to the intrinsic emotional properties of this system, which encompasses the continuum spreading from the VTA to the NA and is potently activated by DA, but many other chemistries too. In this region, DA is thought to promote high frequency gamma oscillations, emerging from deep limbic zones and diffusing across basal ganglia-thalamo-cortical circuits (Alcaro et al., 2007). The activity along this trajectory promotes a basic impulse with a positive hedonic tone to investigate and interact with the environment. This exploration activity is driven by a curious, energized, expectancy state in which organisms are motivated to make sense of their surroundings and anticipate its resource potential. For instance, research in rats has shown that motor and locomotor activity increases when animals enter a place of familiarity, or where previous social or rewarding experiences have been had. This activity involves excited sniffing and vigorous searching of oddities in the environment (Panksepp, 1998) and is accompanied by 50-kHz vocalizations, which are now
commonly accepted to reflect a positive internal state (Brudzynski, 2007) and also occur during other pleasurable activities such as during rough-and-tumble play (Panksepp, 1998). The administration of DA has been found to spontaneously induce this psychobehavioural response in rats, and is reversed by D1D2 receptor antagonists (O’Neill, Dourish, & Iversen, 1991). Likewise, mesolimbic DA has been found to increase in response to novel unconditional stimuli (De Leonibus, Verheij, Mele, & Cools, 2006) and anticipation of reward. For example, in male rats, the sniffing of female urine stimulates DA in the NA (Malkesman et al., 2010).

The vast majority of research done on this region has focused on phasic DA activity and its effects on learning and reward, as measured by self-stimulation and conditioned place preference paradigms (Alcaro et al., 2007). Rats rapidly learn to self-administer various chemicals that act on receptors in the DA system (Ikemoto, 2010), sometimes self-stimulating to the point of exhaustion (Panksepp, 1998). Correspondingly, they develop preferences for locations associated with DA administration (Spyraki, Fibiger, & Phillips, 1982), indicating learning via reward mechanisms. However, when DA transmission is blocked, these learning effects are mitigated (Wise & Schwartz, 1981). Of course, the addictive properties of psychostimulants such as cocaine and amphetamine underlie their initial allure for human subjects. Importantly though, this kind of reward has been differentiated from those that are associated with consummatory pleasures, which in fact, have been found to shut off neuronal SEEKING activity. For instance, in rats, recordings of electrical activity in this trajectory have shown that neurons aroused prior to the administration of food, shutdown during feeding (Hamburg, 1971). Instead, the ML-DA system appears to underpin appetitive drive, which ensures a global, but flexible, state of psycho-behavioural approach (Ikemoto, 2010), sustained by the formation of incentive representations (Ikemoto & Panksepp, 1999). Indeed, DA has been linked to active behavioural coping (Alcaro et al., 2007) and is thought to
underlie innately positive feelings of agency and engagement (Zellner et al., 2011), promoting expectant ruminations and positive excitement (Alcaro & Panksepp, 2011).

The down-regulation of the SEEKING system that is characteristic of the despair phase of social loss, provides a brain model of depression that closely represents the subjective and physiological reality of the condition. In support of this hypothesis, there is a substantial body of evidence linking reductions in DA to animal models of depression, and which align the neurophysiological and behavioural phenotypes of despair with core features of a variant of clinical depression in which apathy and amotivation figure most prominently.

Animal models of depression tend to be organised around the two major symptoms of clinical depression, namely, anhedonia and depressed mood, both of which have been linked to hypo-functionality in DA systems (Alcaro & Panksepp, 2011). Validity of these models tends to be judged on the basis of the efficacy of known antidepressant treatments, provocation by etiological factors thought to be involved in human cases, and finally, similar neurochemical foundations (Nemeroff & Owens, 2002).

Dysregulation of neural activity along the SEEKING trajectory appears to underlie anhedonia and amotivation (Alcaro et al, 2007) and is markedly reduced in response to appetitive novelty and stress in behaviourally depressed animals (Harro, Kanarika, Matrova, & Panksepp, 2011; Stone, Lehmann, Lin, & Quartermain, 2007). Research has indicated that serotonergic and noradrenergic medications which alleviate depression in animal models exert their therapeutic effects via adaptations at the level of the mesolimbic DA system. For instance, chronic desipramine, a tricyclic antidepressant, has been shown to potentiate somatostatin-induced DA release in the NAc in rats (Pallis, Thermos, & Spyraki, 2001), while many others enhance the sensitivity of DA D2-like receptors in this same region, underlying their therapeutic efficacy (Gershon, Vishne, & Grunhaus, 2007). Repeated treatment with antidepressant drugs enhance DA agonist-induced locomotor hyperactivity in
rats (Maj, Rogóz, Skuza, & Sowinska, 1984). In animals, reduced response rates to electrical self-stimulation of DA-mediated reward sites or an increase in the amount of current required to sustain operant responses has been used to infer anhedonia (Anisman & Matheson, 2005). Failure to cope with unpleasant stimuli results in a syndrome of helplessness and motivational blunting, and is linked to reduced mesoaccumbens DA (Cabib & Puglisi-Allegra, 1996). These effects, most often induced experimentally by chronic stress, are attenuated by administration of treatments which systemically increase DA activity (Zacharko & Anisman, 1991). Other research has shown that this diminished reward responsiveness is underpinned by reductions in D2 DA receptor function in the NAc (Klimke et al., 1999) and applies equally to other natural rewards such as highly prized foods (Willner, Towell, Sampson, Sophokleous, & Muscat, 1987). Since DA release in the NA is implicated in motivation and reward, these findings are not surprising. The mechanism underpinning this phenomenon is likely the role of dopaminergic neurons in labelling and predicting the appetitive value of environmental rewards (Ikemoto & Panksepp, 1999), such that low DA transmission translates into a reduction of interest in the pursuit of cues that signal reward. This is consistent with numerous other animal studies showing that a reduction in DA reduces the willingness to work for reward (Salamone, Correa, Farrar, & Mingote, 2007). Also, drugs that act on DA transmission are effective in reversing the effects of Tetrabenazine, which alters effort-based choice in rats, making animals choose the lower effort activity. These findings lend support to the hypothesis that drugs that enhance DA transmission may be effective at counteracting effort-related depressive symptoms such as anergia, psychomotor retardation and fatigue in humans (Yohn et al., 2016).

The presence of ‘depressed mood’ in animals has evidently posed a greater challenge for research models; however, the phenomenon of ‘learned helplessness’ has commonly been used to infer a state that most closely represents the human symptom of hopelessness that
forms part of this criterion. Here, hopelessness is thought to represent the inevitable sense of impotence that is experienced as part of the subjective reality of despair (Alcaro & Panksepp, 2011) and in animals, is epitomized by a failure in active coping. The forced swim test in which animals are placed in an inescapable cylinder of water is a commonly used procedure to induce depressive-like states in rats. Although its validity as a proxy for psychological despair has been questioned (Holmes, 2003), studies indicate that circumstances that predispose a depressive state in humans commonly increase immobility in these tasks (Barr & Markou, 2005) and are associated with depletion of DA in the caudate nucleus and NA (Dunlop & Nemeroff, 2007). The experience of learned helplessness may be related to uncoordinated activity between the midbrain/diencephalon and the limbic forebrain (Shumake, Conejo-Jimenez, Gonzalez-Pardo, & Gonzalez-Lima, 2004) and furthermore, cross-species data show that areas known to actively inhibit activity in this network, are hyperactive in depressed animals (Alcaro et al., 2010). Furthermore, known antidepressant medications are effective in reinvigorating locomotor activity in the forced swim test (Thompson et al., 2004), an effect which appears to be mediated by activation of D2-like receptors (Barr & Markou, 2005) and which can be inhibited by D2 / D3 antagonists (Basso et al., 2005).

The use of genetically vulnerable rodent strains is particularly important in animal models of depression, since in most human cases, MDD probably results from an interaction between environmental and genetic factors (Kendler, Neale, Kessler, Heath, & Eaves, 1992). Rats bred for a genetic vulnerability to depression, specifically, the Flinders Sensitive Line, who show anhedonia and other symptoms associated with depression such as reduced appetite and behavioural responsiveness, and increases in REM sleep, are known to have low extracellular levels of DA in key reward sites (Friedman et al, 2007) and display reduced mobility on the forced swim test (Overstreet, Pucilowski, Rezvani, & Janowsky, 1995).
Similarly, the C57BL/6 strain of mice, bred for their susceptibility to despair, show a much stronger activation of mesocortical DA metabolism in response to stressors, leading to an inhibition of mesoaccumbens DA release (Ventura, Cabib, & Puglisi-Allegra, 2002). These findings implicate a dysregulation of the stress-induced activation of cortical DA in predispositions to depressive states. The DA system is especially vulnerable to powerful homeostatic influences that exert compensatory effects for imbalances in DA levels (Belujon & Grace, 2015). Tonic DA controlled via prefrontal cortical glutamatergic afferents, and released in response to stress, determines the level of responsivity to phasic DA (associated with environmental reward). As such, chronic stress may be capable of reducing the amplitude of DA reward responsivity within subcortical sites (Grace, 1991), underpinning the observed reductions in motivation and interest in pleasurable activities seen in depression. Since the stress-facilitated release of tonic DA may function to support active psychobehavioural coping, consequently it is not observed in uncontrollable situations in which animals are compelled to ‘give-up’ in despair (Cabib & Puglisi-Allegra, 1996). The important role that VTA dopamine neurons play in mediating stress responses was reaffirmed by Chaudhury et al. (2013) who demonstrated neural-circuit-specific mechanisms of depression. That is, phasic activation of VTA neurons projecting to the NAc, promotes susceptibility to stress; optogenetic inhibition of VTA-NAc projection promotes resilience and inhibition of the VTA-medial prefrontal cortex (mPFC) promotes susceptibility. Moreover, longitudinal studies in rats have indicated that DA activation in the prefrontal cortex in response to chronic social stress during adolescence leads to higher density of DAT (dopamine transporter) in the infralimbic area of the medial prefrontal cortex which may underpin behavioural alternations observed in adult life (Novicka, Forstera, Tejani-Buttb, & Watt, 2011). DAT functions to clear synaptic DA and may therefore underlie the reduced levels of DA content reported in these regions. Preclinical studies show that exposure to early
life stress alters VS and NA DA responses to stress in later life (Jahng et al., 2010). This kind of research adds to the growing body of evidence implicating adolescence as a particularly vulnerable developmental period for the DA system (Caballero, Granberg, & Tseng, 2016; Wahlstrom, Collins, White, & Luciana, 2010); in particular, a developmental surplus followed by the pruning of DA receptors (in both humans and rats), and an alteration in the balance between mesocortical and mesolimbic DA systems (Spear, 2000).

Moreover, increases in VTA DA neuronal activity, in particular with regards to NA projections, have been shown to predict social behaviour in mice (Gunaydin et al., 2014). More recently, Matthews et al. (2016), identified a functional role for DRN DA neurons in states of loneliness. Specifically, social contact following isolation resulted in an increase in DRN DA activity and that these same neurons were implicated in ‘rebound sociability’ following an acute period of isolation.

Together, these findings position DA as a key mechanism in animal models of depression. Evidence from a variety of sources extends this idea to support the proposal that depression might best be conceptualised as a state of reduced activity in global SEEKING networks, as is observed following social loss in despair. However, since psychologically valid animal models can only be developed once the pathophysiological matrix of human depression is better understood (Nestler et al., 2002), this poses a great challenge for depression research. Nonetheless, investigations of the brain basis of depression in animals have provided an invaluable paradigm for directly manipulating variables that would otherwise be highly unethical in human subjects. Specifically, this line of research has contributed quite considerably in elucidating some of the proposed pathophysiological mechanisms underpinning the etiology of depression, in which aberrant DA activity emerges as a principal mechanism. Preclinical research has also generated a great deal of knowledge about emotional and stress-related changes in the brain that could not be obtained in other
ways. However, animal-based research cannot access the higher order and abstract thoughts that make up our complex and elaborate mental lives (Panksepp, 2010) and the core subjective features of MDD remain inaccessible in this line of investigation. More specifically, with regard to the current theoretical framework, the central psychic features of the SEEKING system will never be modelled successfully in nonhuman subjects, rendering animal models somewhat inadequate in this approach to depression. Although subjective feelings can be indirectly measured on the basis of affective vocalizations in animals (Panksepp, 1998), when it comes to unravelling the subjective experience of clinical depression, which in humans is a highly cognitive process, and within the current framework likely valenced with feelings of loss emerging from PANIC/GRIEF, animal models can be limiting (Watt & Panksepp, 2009). The insights derived from animal work must be endorsed in human research where self-reported changes and experiences can be recorded (Panksepp, 2005c). Research in humans therefore has the advantage that subjects can uniquely express their feelings, making the diagnosis and monitoring of ‘depressed mood’ more reliable and valid. Human studies consequently have a fundamental role to play in triangulating findings in the field, and in fact, the evidence from the clinical research has paralleled many observations in the animal literature with regard to the dopaminergic hypothesis of depression. What follows is an overview of some of the clinical research trends on DA and its role in depression.

**Human research: Dopamine.** Post-mortem studies point to changes in D2/3 receptor and lower DAT binding in the amygdala of depressed subjects (Klimek, Schenck, Han, Stockmeier, & Ordway, 2002) and decreased expression of D4 DA receptor messenger RNA in the lymphocytes in patients with MDD (Rocc et al., 2002). Reward processing is dependent on tonic DA levels and phasic DA in mesolimbic structures. The ability to assess the value of rewards and to anticipate future rewards has an effect on the motivation to
participate in goal-orientated behaviour (Zisner & Beauchaine, 2016). Thus, reward learning is often disrupted in depressed patients, in particular those with elevated anhedonic symptoms, and is a predictor of outcome (Vrieze et al., 2013). Tremblay et al. (2005) confirmed previous findings that MDD patients experience enhanced dextroamphetamine-induced rewarding effects (for example, euphoria and increased energy) compared with controls. The reward scores of patients in this study correlated with underlying changes in brain activity in DA-rich regions such as the prefrontal region, caudate and putamen. Furthermore, Grace (2016) reported that prefrontal cortical-amygdala hyperactivity reduces reward-related DA neuronal activity leading to anhedonia in depression.

There is a substantial literature on DA and depression in patients with Parkinson’s Disease (PD). The depression that commonly accompanies PD is marked by an absence of gamma wave activity, thought to represent SEEKING impulses (Alcaro et al., 2007), in the basal ganglia-thalamo-cortical circuits (Brown, 2003). This absence of DA is corroborated by findings frequently reporting reduced levels of homovanillic acid, the main metabolite of DA, in the CSF of clinically depressed patients (Kapur & Mann, 1992; Reddy, Khanna, Subhash, Channabasavanna, & Rao, 1992). Dopaminergic and noradrenergic innervation of the VS is implicated in both endogenous and PD depression, and in particular apathy (Remy, Doder, Lees, Turjanski, & Brooks, 2005). The association between apathy and reduced striatal DAT levels in PD patients was again recently demonstrated by Santangelo et al. (2015). The lower DAT binding potential in striatal regions in depressed patients is consistent with a downregulation of DAT in response to a DA lowering process (Meyer et al., 2001). Frisina and Libow (2008) reported a seven times greater nigral neuronal loss in post-mortem brains of PD patients with depression compared to non-depressed PD patients. Furthermore, L-dopa treatment has been shown to improve motivation in some Parkinson’s patients (Czernecki et al., 2002). Chong et al. (2015), demonstrated how DA improved motivational deficits in PD
patients by promoting willingness to exert effort. However, in a review by Jaunarajs, Angoa-Perez, Kuhn, and Bishop (2011), L-dopa treatments did not reliably improve affect in PD patients, and in some cases (Hanganu et al., 2014), affect was worsened. The authors suggest that this was possibly due to the depletion of NE and 5-HT levels consequent to DA processes.

DA release in the VS in response to *psychosocial stress* is elevated in humans with poor quality early life maternal care. Pruessner et al. (2004) reported that exposure to psychosocial stress increased markers of extracellular DA in the VS in a manner that was correlated with increased cortisol release. Similarly, Oswald et al. (2014) showed that childhood adversity and high levels of perceived stress were each associated with higher VS DA responses to amphetamine.

There are numerous studies that report promising results from *deep brain stimulation* in depressed patients. DBS of (a) the subcallosal cingulate gyrus in patients with treatment resistant depression (TRD) has resulted in significant decreases in depression scores at 1 year post intervention (Lozano et al., 2012); (b) the ventral capsule/ventral striatum, where 35% of TRD patients in a study conducted by Malone et al. (2009), remained in remission at an average of 37 months follow-up; (c) the NA, where the core symptoms of clinical depression, particularly anhedonia, were relieved (Bewernick et al., 2010). In a study by Schlaepfer et al. (2008) patients undergoing stimulation in this region spontaneously reported desires to engage in activities which had previously been considered pleasurable. Of note though, the authors described these phenomena as “unprompted behavioural responses” (p.372), indicating an essential neglect of the intrinsic motivational properties of feelings in these kinds of statements; and lastly, Schlaepfer, Bewernick, Kayser, Mädler, and Coenen (2013), reported that bilateral stimulation of the superolateral branch of the medial forebrain bundle was efficacious in rapidly reducing symptoms in TRD. In this instance, the easing off of
depressive symptoms argues Panksepp (2014b), is attributable not to aroused sensory hedonics, but to aroused states of enthusiasm, with resultant positive engagement in social activities. In this regard, Boccard et al. (2014) argue that brain stimulation contributes to an improvement in mood by attenuating negative affective states and (d) hypomania can be induced following STN DBS, along with the left-sided co-activation of the medial forebrain bundle (MFB) which leads to the activation of Panksepp’s SEEKING system (Coenen et al., 2009).

Human studies have also demonstrated a particular role for the VS in aspects of aversive motivation and learning. Specifically, war veterans with post-traumatic stress disorder showed increased blood flow in VS/NA in response to the presentation of aversive stimuli (e.g. combat sounds; Liberzon et al., 1999). Similar findings were reported by Niznikiewicz and Delgado (2011), who demonstrated that ventral striatal BOLD responses were increased during aversive conditioning to a primary aversive stimulus (shock) as well as monetary loss. Likewise, Baliki, Geha, Fields, and Apkarian (2010), reported that in normal subjects, phasic BOLD responses occurred both to the onset and the offset of a painful thermal stimulus. Elevated ventral striatal BOLD responses have also been reported in response to prediction errors regardless of whether the stimulus predicted rewarding or aversive events (Jensen et al., 2007), and aversive prediction errors have been blocked by the DA antagonist Haloperidol (Menon et al., 2007). Although many studies have indicated that mesolimbic-mesocortical DA activation correlates with loss aversion, Voigt, Montag, Markett, and Reuter (2015), reported that loss aversion could be related specifically to genetic differences in DA functioning. They found that subjects who carried the allelic constellation 66Met+/A1+, which is characterized by a relatively low D2/3 receptor binding in the striatum, displayed the lowest loss aversion. Furthermore, an improvement in apathy in brain damaged patients following treatment with DA agonists has been demonstrated by
Blundo and Gerace (2015). Along similar lines, Farinelli et al. (2013) showed that patients with lesions in the anterior medial subcortical-cortical regions, displayed lower SEEKING (as measured by the Affective Neuroscience Personality Scale (ANPS) and higher depression scores. Lastly, Volkow et al. (2007) reported that reduced DA activity in the caudate and limbic areas in adults with Attention Deficit Hyperactivity Disorder (ADHD) was associated with inattention.

The role of DA in depression has and continues to be well-explored but what is clear from some authors is that they still adopt a fundamentally cognitivist appreciation of ‘depressed mood’ in which feelings of hopelessness and worthlessness are attributed to neocortical structures (Nestler et al., 2002). The burden of a shift in this kind of corticocentric thinking is required and will rest upon new evidence clarifying the intrinsic intentionality of SEEKING dynamics, supporting the direct relationship between subcortical structures and subjective feelings (Alcaro et al., 2007). Human studies using pharmacological stimulation of SEEKING and PANIC/GRIEF networks are needed in order to corroborate the brain foundations of depressed mood, and aid tremendously in addressing the question of where the primal affective feelings of ‘worthlessness’, ‘hopelessness’ ‘despair’ and ‘emptiness’ might emerge.

**Pharmacological research and the subjective experience.** Surprisingly, despite a considerable amount of research, the question of subjective feelings has not been adequately addressed. With regards to DA, much of the work has focused on the efficacy of DA agonists developed for treating clinical depression, and as such, relies largely on formal diagnostic criteria such as those stipulated in the DSM, and which do not look specifically at qualitative changes in subjective affect. Nonetheless, research has shown that many DA agonists, such as bromocriptine, bupropion, ropinirole, pramipexole and nomifensine have antidepressant effects (Treadway & Zald, 2011). For instance, chronic pramipexole treatment has been
shown to enhance the positive subjective effects (in particular, feeling stimulated) produced by cocaine (Newton et al., 2015) and to reduce the severity of depression and anhedonia in Parkinson’s patients (Lemke, Brecht, Koester, & Reichmann, 2006). More recently, Fawcett et al. (2016) reported favourable and lasting (16-month follow-up) clinical responses to pramipexole in 75% of their patients with treatment resistant depression.

Descriptions of subjective effects are more commonly cited in studies on psychostimulants. Selective DA manipulations can alter subjective pleasurable responses (such as ‘arousal’, ‘elation’, ‘vigor’) to psychostimulant drugs as evidenced by self-report measures (Brauer & de Wit, 1996; Romach et al., 1999). This body of research has indicated that feelings of euphoria (amphetamine administration; Martinez et al., 2003) and arousal/stimulation (cocaine administration; Schlaepfer, Pearlson, Wong, Marenco, & Dannals, 1997), underpin their appeal in human subjects (Johanson & Uhlenhuth, 1980). Others have also reported sexual arousal, love, happiness, peace and a sense of connection (Cohen, 1995). Drevets et al. (2001) demonstrated how the euphoric response to dextroamphetamine correlated positively with the magnitude of DA release in the anteroventral striatum, demonstrating how a stimulated SEEKING system leads to an increase in “enthusiastic positive excitement”.

Psychostimulants are known to exert their effects through the mesolimbic DA system. Specifically, their reinforcing effects are associated with increases in DA, especially in limbic areas such as the NAc, by either binding to the DA transporter to inhibit DA reuptake (as in the case of cocaine and methylphenidate), or to cause reverse transport of DA via the DA transporter (as in the case of amphetamine). Recent evidence also points to the involvement of non-dopamine transporter-mediated mechanisms of DA release by psychostimulants involving norepinephrine transporters in the prefrontal cortex (dela Peña, Gevorkiana, & Shi, 2015). However, it is important to note that psychostimulants can also act on opioid and
serotonin systems (Soderman & Unterwald, 2009; Urban et al., 2012). Serotonergic networks are implicated in cocaine addiction (Burmeister, Lungren, Kirschner, & Neisewander, 2004) and methamphatamine can increase serotonin receptor levels (Berger, Gu, & Azmitia, 1992). There is also considerable evidence for the role of norepinephrine, GABA and glutamate in the subjective positive effects of psychostimulants (Zack & Poulos, 2009). This may partially explain why results from human studies do not consistently show that DA antagonists are successful in attenuating the subjective effects of d-amphetamine. For example, pimozide does not appear to inhibit the self-reported experience of arousal and elation following d-amphetamine administration in healthy subjects (Jacobs & Silverstone, 1986 in Brauer, Goudie, & de Wit, 1997). On the other hand, risperidone has been shown to attenuate some subject-rated effects of d-amphetamine, confirming the notion that monoamine systems do influence the behavioural effects of methamphetamine in humans (Rush, Stoops, Hays, Glaser, & Hays, 2003). Similarly, the DA antagonist ecopipam has been shown to attenuate the euphoric and stimulating effects of cocaine (Romach et al., 1999).

Furthermore, many studies rely solely on established psychometric scales in the assessment of subjective feelings, such as, to mention but a few, the ‘Addiction Research Center Inventory’ (Jasinski, Johnson, & Henningfield, 1984) or behavioural measures such as the ‘Brief Psychiatric Rating Scale’ (Bossong et al., 2009). Others, like Rutledge, Skandali, Dayan, and Dolan (2015), use computational models to assess the subjective effects of DA on momentary happiness associated with the receipt of rewards. While findings of ‘vigor’, ‘elation’, ‘arousal’ and ‘positive mood’ have been unequivocal across subjects in response to amphetamines (Johanson & Uhlenhuth, 1980), little room has been left for more qualitative accounts of self-reported emotional experiences. Moreover, many of these studies make use of retrospective data from regular drug users (Cohen, 1995), making inferences about the functioning of the normal DA system less generalizable.
With regards to opioids, the vast majority of research on the pharmacological properties of µ-opioids in humans has focused on their analgesic effects in the treatment of physical pain. Subjective effects have become a point of interest because of the potentially addictive consequences of opioid administration, and research here has reported that tramadol, a pain medication with moderate affinity for the µ-opioid receptor, enhances subjective ratings of ‘liking’ and feeling ‘high’, which have been linked to their reinforcing effects (Babalonis, Lofwalla, Nuzzob, Siegelc, & Walsh, 2013). Likewise, morphine and oxycodone, both mu agonists, have been shown to increase subjective feelings of being ‘in control’, ‘relaxed’, ‘sedated’, ‘carefree’ and ‘elated’ (Wightman, Perrone, Portelli, & Nelson, 2012; Zacny & Lichtor, 2008). In contrast to most observations, some research has failed to report on the euphoric effects following µ-opioid manipulation. Wagner et al. (2010) observed an increase in negative affect following administration of remifentanil which is known to promote µ-opioid activity. These discrepancies might be accounted for by multiple opioid systems and that pharmacological manipulation will invariably affect many systems that are not related (Nelson & Panksepp, 1998). Sex differences have been reported in µ-opioid receptor concentrations, for example, deactivation of µ-opioid neurotransmission in NAc, in women, in response to painful stimuli (Zubieta et al., 2003). Furthermore, the menstrual cycle influences neuroendocrine responses to opiate manipulation (Hohehe et al., 1988).

As in the pharmacological literature on DA, most studies on opioids employ fixed response formats in the exploration of subjective emotional effects, and consequently, they are only as useful as the questions that they ask and the theoretical orientation of the researcher. This issue has been addressed to some extent in a study that investigated the antidepressant effects of Buprenorphine, which is a partial µ-opioid agonist that has κ-opioid antagonist properties, and subsequently prevents addiction (Bodkin, Zornberg, Lukas, &
Cole, 1995). Although assessments of clinical depression were measured using standardized criteria, the authors provided detailed, qualitative reports of the experience of participants’ remission from depression. These accounts indicated that buprenorphine was remarkably successful in promoting feelings of subjective well-being and alertness and improving sociability, goal-directed intent and behaviour and sleeping patterns. Additionally, they reported increases in feelings of ‘elation’, ‘friendliness’ and ‘vigor’ on the widely used Profile of Mood States.

The significance of the Bodkin study is that it highlights the central role of social chemistries in the maintenance of depressive affect. Adopting this theoretical standpoint helps to interpret findings from studies reporting feelings of being ‘in control’ and ‘care free’ (Zacny & Lichtor, 2008), which may relate directly to brain affective systems that mediate attachment and social bonding, promoting feelings of security and social warmth. Furthermore, since µ-opioids have been shown to increase DA in the NA (Koob, 2008), this may underlie their stimulating effects on motivated goal-directed behaviour.

To summarize, subjective reports of the chemistries that promote and antagonize the µ-opioid and DA systems are sparse and usually carried out within constricting experimental designs. There is therefore a pressing need for data that describes succinctly these human subjective homologues of established basic emotion systems. In other words, we need to establish in human subjects, that SEEKING will be able to counteract the psychic pain caused by a protracted and overactive PANIC/GRIEF system (Panksepp & Yovell, 2014). This data will contribute in an important way to understanding the uniquely human experience of clinical depression, which is typified by higher mental processes of rumination and the like that become layered upon the more basic, prototypical affect states that underlie mammalian despair, and which have informed, undoubtedly, by the current criteria by which we define the condition.
Psychodynamic Perspectives on the Subjective Experience of Depression

Notwithstanding its many critics, the psychodynamic tradition has at least always taken seriously the subjective aspect of mental disorders. The classic text in the present context is of course Freud’s. As previously mentioned, Freud (1917) was the first to draw attention to the close similarity between clinical depression (‘melancholia’) and normal grief (‘mourning’). He suggested that mourning and melancholia are both responses to the loss of a love object. In mourning, the loss is clearly identifiable, and the mental work of grieving enables recovery from the loss. In time, the reality of the loss is accepted and clinging to the lost object ceases, as despair ends, enabling the process of finding a new object. However, in melancholia, the loss is not accepted or even fully acknowledged; ‘reality-testing’ remains a struggle and separation from the lost object remains incomplete. Thus, despair may persist indefinitely (in Freud’s theory, anger towards the ‘abandoning’ object is an additional major factor, but this aspect is not pertinent to the present study).

Some have argued that the neglect of the critical mediating role of such abstracted and symbolic mental representations and systems of meaning in depression remains a fundamental challenge to the prevailing reductionist research enterprise (Blatt & Luyten, 2009). It has long been recognized in the psychodynamic literature that the interpersonal interpretive mechanisms that process the self in relation to significant others, commonly referred to as internal working models (Bowlby, 1969), may constitute the fulcrum of depressive states. Self-monitoring or ‘conscious metacognition’ (Joensson et al., 2015) is partly regulated by DA. Indeed, recent findings from neuroimaging support these intuitive ideas, indicating that overactivity in the cortical midline structures (default mode network – DMN), specifically area 25 of the cingulate cortex, which are thought to be involved in self-referential processing, may contribute to depressive feelings. Specifically, these authors report that when activity in this area is inhibited, patients spontaneously report a sense of
social connection and warmth (Mayberg et al., 2005). Importantly, DA appears to help in deactivating the DMN (Delaveau et al., 2010; Tomasi et al., 2009). Moreover, acute stress leads to an increase in DA release in the prefrontal cortex (PFC) which in turn dampens DA release in the NA (Shippenberg, et al., 2007), whereas prolonged stress attenuates baseline DA release in the PFC (Goto, Otani, & Grace, 2007). The bi-directional nature of DA changes may provide a mechanism via which clinical depression is sustained. Thus, the implication here is that cortical-self-referential processes may play a prominent role in influencing DA activity via its role in stress-related DA activation in the PFC, and may also explain why, once the self is ‘impoveryed’ (Freud, 1914), a cycle of depression is maintained in a synergistic fashion by both cortical and subcortical processes. Self-referential processing in this context is described by Northoff et al. (2006) as the ‘experiential self’, or ‘core-self’, that is, the basic way in which we reflect on our own individual experiences, and this level of processing may be subserved by an even more fundamental and affective level of processing which relates to the subjective experience of internal and external stimuli. Neuroimaging studies show that self-referential processing is mediated by cortical midline structures, which are reciprocally connected to subcortical midline regions, and in particular, the anterior cortical midline structures which are implicated in depression (Lemogne, Delaveau, Freton, Guionnet, & Fossati, 2012). SEEKING is essential to self-experience as it promotes interaction with the external world, allowing for the objectification of internal needs (Alcaro & Panksepp, 2011). This could be linked with the ‘giving up’ response in depression, and with Bibring’s (1953) concept of ‘learnt helplessness’.

Psychodynamically, all types of distress, including separation distress, lead to the enlisting of cognitive-affective schemas to mediate such distress (Blatt & Luyten, 2009). An analysis of the affective schemas that characterise the depressive mind may -- as such -- go a long way in elucidating the primary process emotions upon which they are elaborated.
The possibility must also be considered that the critical role of area 25 represents its connectivity not only with the SEEKING system but also (more directly, in fact) with the PANIC/GRIEF system itself. Panksepp (1998) summarizes the data implicating area 25 in the ‘protest’ phase of separation distress.

A shortcoming of the psychoanalytic tradition is the empirical gulf separating it from the mainstream of modern psychiatric and neuroscientific research on depression. Kandel (1999) proposed that one reason for this hiatus is that psychoanalysis has not adopted a scientific or empirically-based methodology to test its ideas, preferring to rely, in most part, on clinical observation alone. Psychoanalysis has not made any significant progress in relation to other disciplines of the mind because it has largely failed to subject its claims to experimental testing and consequently has now lost the influence it enjoyed in the first half of the twentieth century. Neuroscience on the other hand continues to make ongoing contributions to the study of the mind by identifying the biological basis for various conscious and unconscious mental processes. This hiatus however is now being filled by ‘Neuropsychoanalysis’; an approach to the study of the mind of particular relevance to the present study, as it recognises not only the biological foundations of the affective mind but also that how we reflect on our individual experiences is subserved by such affective foundations (Solms & Turnbull, 2011). Solms (1997) and Kaplan-Solms and Solms (2000) pioneered this approach by studying the subjective effects of focal brain lesions using psychoanalytic methods and theories. Solms and Turnbull (2011) have made the point that, in principle, the same could be done using pharmacological probes (as opposed to lesions) to examine the subjective experience of psychotropic medications, which is what the current thesis explored.
Specific Aims and Rationale

It is evident from the preceding review that a satisfactory model of depression has not been established, especially one that accounts for the ‘felt’ aspects of this disorder in relation to its neural underpinnings. It is, after all, the psychological pain of depression - the hopelessness, despair, and loss of motivation - that define it, rendering many individuals emotionally, and in some cases, even physically stuck. The separation-distress model of depression attempts to address this. It accounts for the way in which depression makes people feel by seeking to identify the specific changes from ‘protest’ to ‘despair’ that lead to the psychological pain and hopelessness associated with depression. It hypothesizes that two mechanisms are implicated in depression: a hypoactive SEEKING system, which can cause a lack of interest in life (‘despair’) and a hyperactive PANIC/GRIEF system, which generates psychological pain (‘protest’). Presently, this conceptualization of the brain basis of depression aligns with the clinical realities of the condition more closely than most (Solms & Panksepp, 2010). Even though there is abundant preclinical literature that supports the separation-distress model of depression, the core human experience of depression remains largely inaccessible in this kind of research. Animal research is foundational as it allows for predictions to be made about affective changes in humans following manipulations similar to those undertaken in this research. The human data that is currently available is minimal and not directly focused on the affective systems of SEEKING and PANIC/GRIEF. *The present study aims to address this hiatus.*

The rationale underlying the current study was to pharmacologically manipulate the SEEKING and PANIC/GRIEF systems in humans for the purposes of (a) generating much needed subjective data that can corroborate the subjective states that could perforce only be *inferred* in the animal studies of separation distress and animal models of depression, and thereby contribute additional insights into the human homologues of the established
mammalian basic emotion systems. This should aid in identifying the neurochemical substrata of the primal affective feelings of ‘worthlessness’, ‘hopelessness’ ‘despair’ and ‘emptiness’, which are so ubiquitous in depression; and (b) begin to assess the influence of ‘attachment’ traits and separation/loss events in relation to the role of the SEEKING and PANIC/GRIEF systems in separation distress. Further insights into the affective dynamics that characterise the depressive mind would go a long way in elucidating the primary process emotions upon which they are elaborated, and the data generated from this study could potentially contribute towards understanding the uniquely human experience of clinical depression. Over and above the use of standardised psychometric measures, the study also employed psychoanalytic techniques to qualitatively explore how each participant experienced social loss following manipulation of the SEEKING and PANIC/GRIEF systems.

The aim of this study was thus to examine the subjective effects of once-off doses of \(\mu\)-opioid agonists and antagonists, dopamine agonists and antagonists, and a placebo, on certain psychological variables, in healthy volunteers. The emphasis of the study was to obtain structured self-report data (both quantitative psychometric data and qualitative psychoanalytic data) in relation to pharmacological manipulations of these affective systems – in other words, to obtain the sort of data that cannot be obtained in animal studies.

Data collection was multi-levelled. In the broader context of the whole sample, the hypothesised medication effects on the psychological variables of SEEKING, PANIC/GRIEF, affective valence and mood were investigated using two approaches: (1) formal psychometrics (questionnaire-based), and (2) informal psychological probes (non-questionnaire-based). In the first approach, all four variables (SEEKING, PANIC/GRIEF, affective valence and mood) were psychometrically quantified, with specific reference to standardised questionnaires. In the second approach, that is, the psychological probes, the
qualitative aspects of some of the variables were further explored and measured. Participants were asked to describe the effects of the five medications upon their subjective state using their own words (‘free association’), to rate any subjective change in SEEKING and PANIC/GRIEF as defined by the investigator (‘directed probes’), and to rate any change in the degree of separation distress experienced when recalling personal memories of social loss (‘memories of loss’).

The separation-distress constructs of ‘despair’ and ‘protest’ were in turn investigated separately. Since the despair phase of the separation distress model is the normal prototype for depression, the sample was split into High and Low depression groups based on the Major Depression Inventory (MDI) scores, where High ‘despair’ was operationalised as a relatively high score on the MDI and vice versa (i.e., High-MDI represents High ‘despair’).

Since ‘protest’ represents a response to separation from an attachment figure, the sample was again split into High and Low-Avoidance and High and Low-Anxiety groups based on scores from an attachment questionnaire, the Experiences in Close Relationships-Revised (ECR-R) scale. The ECR-R has two sub-scales: avoidance and anxiety. Thus High ‘protest’ was operationalised as High-Avoidance and/or High-Anxiety and vice-versa.

The same four psychological variables (i.e., SEEKING, PANIC/GRIEF, affective valence and mood) were investigated in the High and Low ‘despair’ and ‘protest’ groups as in the whole (undivided) sample. Formal statistical analyses were carried out on this data.

The following heuristic predictions were investigated:
For the whole sample.

Hypothesis 1: A dopamine agonist (Madopar) will significantly increase SEEKING\(^3\) and positive affect (PA) and significantly improve depressive mood (MDI) on psychometric testing, relative to baseline. Madopar will likewise increase SEEKING and improve affective valence and mood as qualitatively described during the *psychological probes* (directed probes, memories of loss and free associations).

Hypothesis 2: A dopamine antagonist (Haloperidol) will significantly decrease SEEKING, increase negative affect (NA) and significantly worsen depressive mood (MDI) on psychometric testing, relative to baseline. Haloperidol will likewise decrease SEEKING and worsen affective valence and mood as qualitatively described during the *psychological probes* (directed probes, memories of loss and free associations).

Hypothesis 3: A µ-opioid agonist (Morphine\(^4\)) will significantly decrease PANIC/GRIEF\(^3\), increase PA and significantly improve depressive mood (MDI) on psychometric testing, relative to baseline. Morphine will likewise reduce PANIC/GRIEF and improve affective valence and mood as qualitatively described during the *psychological probes* (directed probes, memories of loss and free associations).

Hypothesis 4: An opioid antagonist (Naltrexone) will significantly increase PANIC/GRIEF and NA and significantly worsen depressive mood (MDI) on psychometric testing, relative to baseline. Naltrexone will likewise increase PANIC/GRIEF and worsen affective valence and mood as qualitatively described during the *psychological probes* (directed probes, memories of loss and free associations).

\(^3\)As defined by Panksepp (1998).
\(^4\)Morphine is primarily a µ-opioid receptor agonist, and acts to a lesser degree upon δ- and κ-receptors. Naltrexone is likewise most potent at the µ-opioid receptor. Levodopa acts on both D1 and D2 receptors and Haloperidol is a D2-prefering receptor antagonists.
For the split samples.

Hypothesis 5: The magnitude of change for SEEKING, PA, NA and MDI on the dopamine-based medications will be significantly different between the low and high baseline-MDI groups (i.e. high and low baseline ‘despair’). The groups will likewise differ in relation to their psychological probes (directed probes, memories of loss and free associations) on the Dopamine-based medications.

Hypothesis 6: The magnitude of change for PANIC/GRIEF, PA, NA and MDI on the opioid-based medications will be significantly different between the low and high baseline-ECR ‘anxious’ and ‘avoidant’ attachment groups (i.e., high and low baseline ‘protest’). The groups will likewise differ in relation to their psychological probes (directed probes, memories of loss and free associations) on the Opioid-based medications.
CHAPTER THREE:

Methods

Research Design

This was an exploratory study, with a double-blind, placebo-controlled, repeated-measures design. The outcome variables (SEEKING, PANIC/GRIEF, affective valence, and mood) were investigated in data derived from both formal psychometric measures (i.e. standardised questionnaires) and informal psychological probes (i.e., non-questionnaire based). The pharmacological intervention consisted of five conditions: µ-opioid agonist and antagonist; dopamine agonist and antagonist; and placebo. The study incorporated one group of healthy individuals who participated in all pharmacological intervention conditions. None of the participants met the diagnostic criteria for depression or anxiety disorders at the time participation in the study commenced. All participants were assessed both on and off medications (that is, at baseline). The order of administration of the pharmacological interventions and placebo (hereafter referred to as the medications) was counterbalanced, as randomization was not possible due to the small sample size. Likewise, the order in which the measures were presented was counterbalanced across participants. Both the participants and the psychoanalyst conducting the interviews were blind to the medications but not to the underlying study hypothesis (i.e., that depressive affect is linked with the dynamics of the separation distress system.). A quasi-experimental design was adopted in order to test descriptive causal hypotheses about pharmacological interventions in the absence of randomization. Specifically, this study was a “one-group pretest-posttest” study, a commonly used type of quasi-experiment (Harris et al., 2006). Quasi-experimental designs are useful in establishing potential associations (Thompson & Panacek, 2006).

This project was undertaken by an assembled team of experts from different specialist fields to assist with various aspects of the study. Firstly, a registered psychoanalyst, Professor
Mark Solms (University of Cape Town; UCT), performed all the psychoanalytic sessions with the participants. This expertise ensured that the most pertinent data was derived from the participants’ subjective experiences and accounts whilst they were on the medications. Secondly, the team included a registered psychiatrist, Dr Tinus Brink (Panorama Hospital, Cape Town), who prescribed the medications to be administered and oversaw the drug administration process during data collection in order to ensure the health and wellbeing of the participants. The research team also comprised a qualified and experienced pharmacologist, Dr Georg Schoenbaechler (University of Zurich), who advised on the specific medication, optimal dosages to be administered and the optimal times at which each of the five medications were to be taken prior to the interview.

**Ethical considerations.** Ethical approval for this study was granted by UCT (see Appendix A) and the study was conducted in accordance with the principles for research with human participants outlined in the Declaration of Helsinki (2008). Participation in the study required a great deal of personal commitment from each subject, both physical and psychological, which raised the issue of cost versus benefit of active participation. Most of the participants were members of professional psychoanalytic associations and were in private clinical practice ($N = 10$). The balance had undergone some form of psychoanalytic psychotherapy. They all had personal experience of the debilitating effects of depression – either through their patients or from their own lives – and were acutely aware of the limitations of current theories and interventions. Therefore, when presented with the opportunity to participate in a study designed to explore a novel approach to the psychodynamics and neurodynamics of depression, centered on the subjective experience, their scientific curiosity prevailed. Moreover, they were aware that their participation could potentially benefit others in future as the results of this study could contribute towards laying the foundations for new approaches to the pharmacological treatment of depression. Lastly,
the psychoanalyst who conducted the interviews was well known to all participants which
greatly allayed their concerns relating to the disclosure of intimate experiences and
confidential information. Every effort was made to minimize discomfort to participants and
to ensure their wellbeing and a medical doctor was on call in the event that participants
experienced any negative side-effect to one of the medications.

**Sample**

A purposive (also referred to as subjective) sampling approach was utilised to identify
potentially suitable participants. This particular type of sampling strategy was necessary since
a certain group of participants was needed who possessed specific skills (e.g., introspection
and psychological vocabulary). Potential participants were mainly sourced from various
professional psychoanalytic organisations. Other participants that were approached were
individuals in private psychotherapeutic practice and individuals who, although not practicing
psychoanalysts or psychotherapists, had been in psychoanalytic therapy for a considerable
period. These individuals, one could reasonably assume, would be very familiar with the
concept of introspection, the need for full disclosure, etc. This was an essential requirement
since the lowest possible effective dose of each of the medications was given and each
medication was only taken once-off. It was anticipated that the possible effects of the
medications on mood would be subtle. It was therefore important that each of the participants
would be able to utilise good insight into their own psychological functioning and, most
importantly, would be able to discern and describe changes in their mood, and at the same
time be able to articulate possible changes in rich qualitative detail. In short, participants were
required who were ‘psychologically-minded’. Furthermore, all the participants that were
approached to participate were previously known to the study’s psychoanalyst. The study
required each participant to share intimate and, in many cases, painful information. The safe
interpersonal relationship between the psychoanalyst and the participant was therefore crucial
to the success of the psychoanalytic sessions. In short, all the participants were familiar with the psychoanalyst, to varying degrees, and felt secure enough to share intimate details of their lives with him.

Nineteen individuals were deemed suitable for inclusion and were willing to participate. There were two central inclusion criteria: (a) Participants were either practicing psychotherapists or had undergone their own psychotherapy and (b) they were physically healthy. Of these 19, three dropped out at various points post enrolment.

**Dropouts.** In total, three of the 19 participants deemed suitable for inclusion dropped out at some point following the first induction session, of these, two were male and one female. The first male dropped out immediately following his induction session (i.e. prior to his first psychoanalytic interview session) because his partner did not feel comfortable with him participating in the study. The female participant withdrew after two of her psychoanalytic interview sessions for emotional reasons, as she reported that she could not, at that time, deal with the emotional effects that the study was having on her home life. Finally, the third participant withdrew from the study at the time of his first psychoanalytic interview session due to the nausea that resulted from taking the DA agonist.

**Final sample.** 16 participants went on to complete the entire study: six males and ten females. The participants ranged in age from 21 to 58 years ($M_{age} = 35\pm11.84$ years). The average male was 30 years of age ($SD = 5.79$), while the average female was 38 years of age ($SD = 13.60$).

**Procedure**

**Recruitment.** All potential participants who volunteered for this study were recruited from the membership of either the South African Psychoanalytic Association, the International Neuropsychoanalysis Society, or the South African Psychoanalytic Initiative, and postgraduate students of the International Psychoanalytic University in Berlin, Germany,
or the Department of Psychology at UCT. The rationale for selecting these participants has previously been described. Participants were first contacted via email to ascertain whether they would be interested in participating. A brief explanation of the nature and the underlying hypothesis of the study was provided. Potential participants were also informed in this introductory email that, should they agree to participate, they would be administered once-off doses of four psychotropic medications in general clinical use and one placebo. Participants who expressed interest in participating were then sent a Health Screening Questionnaire (Appendix B), so that their physical suitability could be confirmed. The primary exclusion criterion was any participant with either a history of pre-specified medical conditions, or who was currently symptomatic, and who could potentially be harmed by any of the medications. These exclusion criteria were: (a) asthma, (b) respiratory or hepatic insufficiency, (c) serious medical conditions (such as renal, neurological, coronary artery disease, circulatory vascular disease, peripheral vascular disease; metabolic diseases; hormonal diseases), (d) any major psychopathology, including affective and psychotic disorders, (e) use of psychoactive medication, (f) previous head injury, (g) any other neurological condition, and (h) pregnancy or lactation. The Health Screening Questionnaires were anonymised and sent to a medical colleague for assessment. None of the individuals who expressed interest in participating were excluded on the grounds of a prohibitive medical condition. Participants were once again contacted via email to set up an appointment for the initial ‘induction’ session. The total number of sessions included one induction and five experimental/psychoanalytic sessions. All sessions took place in the Psychology Department at UCT. All sessions were audio recorded and the interviewing psychoanalyst also recorded, in writing, each of the sessions.

**Induction.** The purpose of the induction session was threefold: (a) Completing and signing of the Participant Information Sheet (Appendix C) and consent forms (Appendix D),
(b) completing baseline psychometric measures, and (c) the recording of three memorable episodes of personal loss that each participant had experienced throughout the course of their lives. This session was conducted with each participant individually and in strict privacy, as were all the other sessions attended by the participants throughout the duration of the study. This induction session provided an introductory forum, where participants were briefed orally, in greater detail, with the aid of the Participant Information Sheet, about the nature and intended purposes of the study. They were also informed of the specific types of medications that would be administered. Throughout this session, participants were afforded the opportunity to ask any questions that they might have. This briefing process included emphasising how all the data to be collected would be kept confidential and that the anonymity of each participant would be ensured. It also involved emphasising to the participants how their participation was entirely voluntary and that they could freely withdraw from the study at any point in time. This was done with the aid of the consent form which each participant then signed.

Stage two of the induction session required participants to complete four standardised questionnaires, described in detail in the ‘Materials’ section. These served as baseline trait measures. The questionnaires administered were the: ECR-R, ANPS, MDI, and the Positive and Negative Affect Schedule (PANAS).

Similar to the protocol adopted by Zubieta et al. (2003), during stage three of the induction session, participants were instructed to focus on three autobiographical events associated with a significant personal loss (for example, the death of a loved one, a romantic break-up, loss of a job). These episodes needed to be established ahead of the five experimental/psychoanalytic sessions, and participants were advised that they would be required to mentally re-experience these episodes during the five subsequent experimental sessions. For this purpose, each of these three episodes were rehearsed and assigned a ‘key’
title which was chosen together by the analyst and the participant. The purpose of the ‘key’
title was to act as a memory trigger of the particular episode for recall during all subsequent
sessions. Stages one and two above were conducted by the principal investigator and stage
three by the psychoanalyst.

Following the induction session, five appointments were made with each of the
participants for the experimental phase of the study. The time-span required to complete the
five experimental sessions varied amongst the participants and was dictated mainly by their
availability. The experimental sessions were booked at least one week apart to ensure that
there were no possible interaction effects between the different drugs. Some participants were
able to adhere to the pre-assigned weekly appointment schedule, but others had to reschedule
some of their dates, thus the time-to-completion of the five experimental sessions varied from
three to six months. Appointments were scheduled for a Saturday morning. The purpose of
this was to firstly not interfere with any participant’s work commitments and secondly, to
ensure that they would have the rest of the weekend to recover from any possible side-effects
they might experience. The medications were delivered to each participant’s home the day
before their scheduled session. Included with the medication were instructions about when to
take the medication and an antiemetic, in the event that they experienced any nausea as a
consequence of taking the medication. It was left to the discretion of each participant to
decide whether the antiemetic was necessary. The time to take the medication was specified
to ensure that it had its peak effect at the time of the session. These specified times varied
according to the medication in question and ranged from one to three hours before the
interview sessions. These times were determined by a qualified pharmacologist and were
based on the time required for peak concentration to be reached after a single dose
administration of each drug. The comfort and safety of the participants was our prime
concern. For this reason, all 16 participants were fetched from their homes for each session
and were driven to the research venue, to ensure that they would not have to drive under the influence of the medications. Likewise, once they had completed their sessions, they were driven back home with express instructions to refrain from any strenuous activity and to not operate a vehicle for the remainder of the day. All participants were blind to the specific medication that they had taken for each of their sessions. Similarly, the psychoanalyst conducting each session was blind to the medication each participant was on, for each of their respective sessions.

**Experimental/analytic sessions.** These sessions entailed two parts: an interview with the psychoanalyst and the completion of four standardised questionnaires. The order in which the participants completed these two parts was counterbalanced. These sessions were designed with two key purposes in mind. Firstly, they served to psychologically probe, qualitatively and via self-report measures (described below), through the session with the psychoanalyst, what the subjective state of the participants was under the influence of each of the psychoactive medications and the placebo. The second purpose was to quantify the emotional states of the participants using various standardised measures, which they also completed during this session (see ‘Materials’ section below). They were: the State Adult Attachment Measure (SAAM), the MDI, the ANPS (abridged, including only the SEEKING and PANIC/GRIEF items), and the PANAS. All of these were current ‘state’ (versus stable ‘trait’) measures. Each session lasted approximately 45 minutes.

**Experimental/analytic protocol.** Depending on the counterbalancing order, participants would, on arrival, either first complete the questionnaires and then proceed to the interview with the psychoanalyst or vice versa.

The interview protocol proceeded as follows. The participant would be escorted to the office and welcomed by the psychoanalyst. Except for their first experimental session, the psychoanalyst would begin each session by doing a general follow up to ascertain how each
person felt during the day/s immediately following their last session. The purpose was to explore if participants experienced any delayed effects of the medication or if they had any further thoughts about or insights into their previous session. Participants were then asked to lie down on the psychoanalytic couch and were asked the open-ended question: “How do you feel right now, under the influence of today’s medication?” The purpose of this question was to encourage participants to freely associate and describe their current mental state in their own words, knowing that their current state was likely to have been altered by a psychotropic medication. Once this process was complete, the psychoanalyst proceeded with asking specific questions, the so-called directed probes, to ascertain whether participants experienced any changes in SEEKING and PANIC/GRIEF since taking the medication. The description of each directed probe was adapted from Panksepp (1998) and outlined below. Participants then had to describe their current affective state in relation to the specific probe and rate any changes on a Likert-type scale, ranging from 0 (no change) to +3 (the largest possible change). 1 was defined as ‘slight change’; 2 as ‘moderate change’ and 3 as ‘extreme change’.

The following identical script was repeated to each participant, on each occasion:

“The drug you have taken may have affected two emotion systems which neuroscientists call ‘SEEKING’ and ‘PANIC’. The emotions associated with these systems can be increased or decreased by the drug you have taken. Please describe how each of the following emotions has been increased or decreased, if at all:

**Increased PANIC** would involve the following types of feelings (these are just examples): “Mental suffering or mental pain of the kind caused by the prospect or experience of separation, loss, or rejection; or the ensuing mental anguish, torment or distress caused by separation, loss, or rejection.”
The participant’s verbal response was recorded, and they were asked to rate the degree of change in ‘increased PANIC’ they felt following the medication, as detailed above.

**Decreased PANIC** would involve the following *types* of feelings (these are just examples): “Feelings of safety and security; warm fuzzy feelings, like being loved and cared about; the feeling of being bonded or attached; and the associated feelings of being confident about the reliability of intimate others and durability of relationships.”

The participant’s verbal response was recorded, and they were asked to rate the degree of change in ‘decreased PANIC’ they felt following the medication.

**Increased SEEKING** would involve the following *types* of feelings (these are just examples): “Wanting to find or discover something; searching or looking for something; feeling inquisitive about or interested in something; actively looking forward to or anticipating something; being positive; being hopeful.”

The participant’s response was recorded, and they were asked to rate the degree of change in ‘increased SEEKING’ they felt following the medication.

**Decreased SEEKING** would involve the following *types* of feelings (these are just examples): “Despair or despondency caused by failure, separation, loss, or rejection; hopelessness or giving up; lack of drive or interest in the world; lack of positive expectation or anticipation; lack of enthusiasm and energy.”

The participant’s response was recorded, and they were asked to rate the degree of change in ‘decreased SEEKING’ they felt following the medication.

The order of the directed probes was counterbalanced. Thereafter, the participants were asked to “mentally travel back” or *re-experience* each of the three episodes of loss that
they had related to the analyst during the induction session. The order of re-experiencing of
the three episodes was counterbalanced. The psychoanalyst would give the participants the
key title of one episode as a prompt, ask them to re-experience this episode in their own
minds, and this was then followed by the instruction to verbally describe and subjectively rate
any change in emotional intensity since the previous time that they had recalled the episode.
The change was rated on a scale, ranging from 0 (no change) to 3 (the highest possible
change in intensity; see above for definitions). Once this scoring had been completed, this
process was repeated for the second and third episodes. Finally, once all three episodes had
been recalled by the participants, the psychoanalyst was required to record his prediction as to
what substance he thought each participant had taken for each experimental session.

At the end of the final psychoanalytic session with the analyst, each participant was
thoroughly debriefed regarding the research process and each was reminded of the study’s
overall goals and the fact that all the data that had been collected was strictly confidential.
Each participant was then given the opportunity to reflect on their individual sessions and
was able to ask any questions that they may have had.

**Materials**

**Measures.**

**Prior to induction session.**

*Health Screening Questionnaire*. This questionnaire was sent to each potential
participant to ensure that they were cleared to enrol on medical grounds. After receiving each
participant’s completed questionnaire, they were anonymized and sent to the study’s
psychiatrist for perusal and comment.

**During the induction session.**

*Participant Information Sheet*. This sheet provided detailed information regarding the
nature and purpose of the study, along with relevant information about the substances that
would be taken. Here, it was clearly specified to the participants that the study would be investigating the effects that the four psychoactive medicines have on the brain, and that the key aims were: (a) to begin to systematically explore the subjective components of some basic emotion command systems that animal models have suggested may be relevant to the phenomena of separation, loss and attachment; and (b) to lay the groundwork for clinical exploitation of this knowledge for the treatment of emotional disorders. The Participant Information Sheet also explained that further requirements would be to complete a set of psychological questionnaires, and to participate in five psychoanalytic interviews with an experienced psychoanalyst. Finally, this sheet informed the participants that the interviews would be audio recorded.

Consent Form. This emphasised that participation in the study was entirely voluntary, and that each participant could withdraw at any point without any consequences. It specified that all the data and personal information would be entirely confidential. It also served to check that each participant fully understood the aims and purpose of this study, and that they knew that they would be required to ingest psychoactive medicines and a placebo substance.

The Affective Neuroscience Personality Scale 2.4 (Davis, Panksepp, & Normansell, 2003). This scale is based on Panksepp’s research and his model of the basic emotion systems and was used as the basis for the directed probes and as a measure of key outcome variables. Seven of the primary-process subcortical brain emotion systems identified by Panksepp (1998) are SEEKING, LUST, ANGER, FEAR, CARE, PANIC/GRIEF and PLAY, and are considered as important foundations of the human personality. Therefore, the ANPS serves as a tool for the assessment of emotional personality by measuring how much of personality variability is related to the strengths and weaknesses of each of these six systems (Davis et al., 2003). It was designed essentially as a research tool with the aim of positioning the adult
human temperament within the primary-process affective systems of the brain (Davis & Panksepp 2011).

The items on all the scales were developed in such a manner as to access feelings and actual behavioural inclinations rather than cognitive social judgments (Davis et al., 2003). The ANPS scale comprises 112 items in total. Each of the basic emotions is represented by 14 items/statements. Filler items are included as validity checks. The ANPS displays good internal consistency for its scales, with reported Cronbach’s alpha values ranging from 0.65 to 0.86 (Davis et al., 2003). With regards to construct validity, the ANPS has been compared with other models of personality, including the Five-Factor Model and Cloninger’s biobehavioural model of personality. The ANPS scores were found to co-vary with FFM scores: SEEKING with openness to experience, PLAY with extraversion, CARE with agreeableness, FEAR and SADNESS with neuroticism, ANGER with neuroticism and low levels of agreeableness (Barrett, Robins, & Janata, 2013). When comparing the ANPS to Cloninger’s Temperament and Character Inventory (TCI; Cloninger, Svrakic, & Przybeck, 1993), Davis and Panksepp (2011) refer to an overlap between ANPS SEEKING and the TCI’s novelty seeking dimension, in that both are DA driven and appetitive.

*Experiences in Close Relationships-Revised (ECR-R; Fraley, Waller, & Brennan, 2000).* This measure is designed as a revision of the original Experiences in Close Relationships (ECR) measure that was first created by Brennan et al. (1998). The ECR-R was then compiled by Fraley et al. (2000). This tool is a self-report measure that is designed to assess adults’ attachment on two subscales of attachment, with the items divided into either the anxiety (i.e. fearing of being rejected and/or abandoned; the extent to which one feels secure vs. insecure about romantic relationships) and avoidance (i.e. disliking intimacy/closeness and not wanting to be dependent on people vs. secure dependence on others) subscales of attachment (Fraley et al., 2000). Security is thus defined as low scores on
both dimensions. The ECR-R is comprised of 36 items that were derived from the same group as for the original tool; 18 Likert-type items that assess romantic attachment anxiety and 18 items that assess romantic attachment avoidance. The findings of research that utilised an item response theory analysis of four different attachment measures were used to select the most appropriate items for the revised tool (Fraley et al., 2000).

The various properties of the ECR-R include sound construct validity (convergent validity and discriminant validity), good test-retest reliability, and good internal consistency, with Cronbach’s alpha values over 0.90 (Fraley et al., 2000; Sibley, Fischer, & Liu, 2005; Sibley & Liu, 2004). ECR-R is preferable in conditions where subtle attachment effects need to be measured with limited statistical power (Sibley et al., 2005). A central principle of attachment theory is that attachment style in adulthood reflects earliest attachment relationships and attachment security is moderately stable across the first 19 years of life (Fraley, 2002). This measure was included in the study as attachment is central to the study’s central hypothesis that, assuming a pre-existing attachment bond, depression may be an abnormal variant of the normal mammalian separation response.

The Major Depression Inventory (MDI, Bech, Rasmussen, Olsen, Noerholm, & Abildgaard, 2001) is a widely used a self-report measure that is used for assessing the symptoms of depression. It was developed by the WHO in conjunction with a Danish psychiatric research group (Bech et al., 2001). The MDI includes the symptoms of major depression in the DSM-IV and the ICD-10 mild, moderate, and severe depression (Bech Timmerby, Martiny, Lunde, & Soendergaard, 2015). Each symptom is rated on a six-point scale, allowing clinicians to assess not only the presence of a depressive disorder according to the DSM-IV and the ICD-10, but also the severity of depressive symptoms (by summing up the scores of all symptoms, with a range of 0 to 50; Bech et al., 2001; Olsen, Jensen, Noerholm, Martiny, & Bech, 2003). It also correlates with other scales that measure the
severity of depression, such as the Hamilton Depression Rating Scale (Olsen et al., 2003). The scores on the MDI range from 0 to 50, with scores between 20-24 indicating mild depression, between 25-29 moderate depression and scores over 30, severe depression. The optimal cut-off score for a diagnosis of Major Depression, as suggested by the authors, is 26 (Bech et al., 2001).

As far as its properties are concerned, the MDI has been found to display adequate internal and external validity, along with adequate sensitivity and specificity by the authors who developed it. Crohnbachs alpha for the MDI is 0.89, which indicates satisfactory reliability (Bech et al., 2001; Cuijpers, Dekker, Noteboom, Smits, & Peen, 2007; Olsen et al., 2003). The question of depression is central to this study; hence the MDI was utilised both as a baseline measure to exclude MDD in participants and as a trait and state measure.

The Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988). The PANAS measures both positive and negative affect and can be used for both trait and state affect. In terms of the dimensions of affect that the PANAS represents, one can distinguish between high PA, involving focus, energy, alertness, enthusiasm, and engagement, and low PA, characterised by lethargy and sadness. In contrast, high NA can be seen to involve fear, anger, guilt, distress, contempt, nervousness and disgust. Low NA will involve serenity and calmness (Watson et al., 1988). The PA dimension reflects a pleasurable engagement with one’s environment while the negative affect dimension reflects personal distress and unpleasurable engagement (Tuccitto, Giacobbi, & Leite, 2009). It has been reported that the NA, but not the PA dimension, significantly contributes towards predicting self-reported anxiety whereas both the PA and NA significantly contribute towards predicting self-reported depression. For example, presentations of anxiety would be characterised by high negative affect, while depression would feature low PA (Tellegen, 1985). Watson, Wiese, Vaidya, and Tellegen (1999) argue that dimensions of the PA and NA represent first-
person components of a more general biobehavioural system of approach (i.e., the positive emotional states of PA are viewed as goal-directed behaviours) and withdrawal (i.e. the negative emotional states of NA encourage cautionary behaviour). Furthermore, the PANAS scales show a significant level of stability over time (from ‘at the moment’ … to … ‘in general’), reflecting the strong dispositional aspect of affect in that one’s mood at a specific moment can reflect one’s general affect (Watson & Clark, 1988). During the induction phase, the PANAS was used as a trait measure and participants were thus instructed to ‘indicate the extent you have felt this way over the past week’ as opposed to ‘right now’. This measure served the purpose of establishing participant’s experience of affect at baseline and it measured the changes in affect after administration of each medication. The PANAS was included as a measure as it is frequently used to gauge changes in emotional states following drug intervention and it has been shown to retain its psychometric qualities even in substance abusers (Soskin, Carl, Alpert, & Fava, 2012; Younger, Zautra, & Cummins, 2009).

The PANAS has good internal consistency, with Cronbach’s alpha values of 0.89 for PA and 0.85 for NA (Crawford & Henry, 2004). Similarly, Watson, Clark, and Tellegen (1988) report Cronbach’s alpha values of between 0.86 and 0.90 for PA, and between 0.84 and 0.87 for NA. In terms of the tool’s discriminant validity, correlation values ranged from -0.02 to -0.18, while for it its convergent validity, the correlation values ranged from 0.89 to 0.95 (Watson et al., 1988). The PANAS has also been shown to be reliable and valid according to Crawford and Henry (2004), who investigated its properties on a non-clinical sample of over 1000 individuals. Its test-rest reliability is sound, with values of 0.79 for PA and 0.81 for NA (Watson et al., 1988). Similarly, they report reliability values of 0.89 for PA and 0.85 for NA (Crawford & Henry, 2004). Finally, in terms of discriminant validity, its two subscales have been shown not to correlate with each other, with reported correlation coefficient values ranging between -0.12 and -0.23 (Watson et al., 1988). The positive
subscale of the PANAS ranges from 10-50 with higher scores indicating higher level of PA. Similarly, the scores on the negative subscale range from 10 – 50, with lower scores representing lower levels of NA.

During the experimental/analytic sessions. Three of the same measures used during the induction session were re-administered during the experimental sessions: ANPS, MDI and PANAS, but this time as state measures. One new state measure, the SAAM, was added.

The PANAS was administered in its original form as it is both a state and trait measure, except that the instruction to participants during the experimental sessions was to ‘indicate to what extent you feel this way right now’, as opposed to ‘over the past week’.

The instruction to participants for the MDI was changed to read: “The following questions ask about how you are feeling right now as opposed to how you have been feeling over the past week”. Each item was also changed to reflect the present tense.

A truncated version of the ANPS (including only the PANIC/GRIEF and SEEKING subscales) was administered. The reason for this was that completing all 112 items on the original ANPS during an experimental session would be too time consuming. As previously mentioned, participants had to complete four questionnaires and an analytic interview in a time period during which a particular medication was at peak plasma levels. To capitalise on limited time, therefore, only two subscales of the ANPS – SEEKING and PANIC/GRIEF – the basic emotions of primary interest in this study, were included. The particular items belonging to each subscale were identified from Davis and Panksepp (2011). Furthermore, the wording of the individual items on these two subscales was amended in such a way that the questionnaire could serve as a measure of state changes, that is, measuring possible changes in feelings ‘at the moment’. For example: ‘I often feel sad’ (original item) was amended to ‘I feel more sad than usual’; ’I rarely think about people or relationships I have
lost’ (original item) was amended to ‘I could more easily now think about people or relationships I have lost.’

The State Adult Attachment Measure (SAAM). The ECR-R was used at baseline as a measure of adult attachment style. However, the ECR-R was explicitly designed to measure stable dispositions as it asks subjects to reflect on their relationships in general, and for this reason, the ECR-R could not easily be converted into a state measure by simply changing the wording or instructions (Gillath, Hart, Noftle, & Stockdale, 2009). The items on the ECR-R are also more likely to access cognitive representations of how people feel about their close relationships and these representations tend to be resistant to change (Greenwald, 1980).

During the experimental stage of the study, we therefore administered an alternative attachment measure, the SAAM, as this is a state measure designed specifically to capture temporary fluctuations in thoughts and feelings. Unlike the ECR, the SAAM explicitly asks participants what they think right now about their attachment relationships (Bosmans, Bowles, DeWitte, De Winter, & Braet, 2014) and is therefore ideal for measuring fluctuations in attachment (Xu & Shrout, 2013). Although attachment style is considered relatively stable (Fraley, 2002; Simpson, Collins, Tran, & Haydon, 2007), several authors have suggested that notwithstanding its stability, attachment can also be influenced by major life events (Cozzarelli, Karafa, Collins, & Tagler, 2003) and diverse contextual factors (Gillath & Shaver, 2007). Attachment styles can be impressionable for very short periods of time such as minutes or hours. For example, reminding someone of a time when they have felt secure or anxious can momentarily override a stable attachment disposition by affecting their perceptions and behaviours (Baldwin, Keelan, Fehr, Enns, & Koh-Rangarajoo, 1996). Hence the SAAM was administered to measure any fluctuations in attachment style caused by the medications. Importantly, it has been demonstrated that the SAAM displays convergent and discriminant validity with the ECR (Gillath et al., 2009; Xu & Shrout, 2013) and to have a
high three-month test-retest reliability. Gillath et al. (2009) report test–retest reliability as being in the range of .51–.59 for each of the subscales. There are three subscales to the SAAM: state security, which reflects feelings of trust and approval; state anxiety, the extent to which one experiences the need to be closer and accepted; and state avoidance, which is a disinclination to intimacy and closeness. All the SAAM subscales have adequate reliability ranging from .83 to .87 and Bosmans et al. (2014) demonstrated that SAAM scores are sensitive to priming effects.

**Medications.** In total, each participant was administered five different substances (four being psychoactive drugs, and one a placebo substance) over the course of their participation. All these substances have been shown in previous clinical studies to be safe and well-tolerated in human subjects.

**Opioid antagonist.** Naltrexone Hydrochloride (Naltima-50, Intas Pharmaceuticals) is a long acting competitive antagonist at opioid receptors with negligible opioid agonist properties, commonly used to treat alcohol and opioid dependence. It has a high affinity for \( \mu \)-opioid receptors (Littleton & Ziegglänsberger, 2003) and acts by inhibiting DA neurons within the VTA and reducing DA function within the NA (Kim, Grant, Adson, & Shin, 2001). Carmen, Angeles, Ana, and María (2004) reviewed 33 published studies published from 1990 to 2002 on the use of Naltrexone for alcohol dependence and found that Naltrexone was safe and acceptably tolerated. Dosages of Naltrexone ranging from 25- to 100-mg have been used in clinical studies (Farren et al., 1999). A dose of 50-mg was administered to participants in this study. This dose has been proven in numerous clinical trials to be well-tolerated (O’Malley et al. 1992; Schmitz, Stotts, Rhoades, & Grabowski, 2001; Volpicelli et al., 1997) and most research on the use of Naltrexone for alcoholism have administered a dose of 50-mg. This dose is also optimal for opiate-receptor blockade (Saitz & O’Malley 1997). The effective half-time for return to baseline opiate receptor occupancy of
50 mg of Naltrexone is 72 to 108 hours (Myung et al., 1988). Following oral administration, Naltrexone undergoes rapid and nearly complete absorption with approximately 96% of the dose absorbed from the gastrointestinal tract. Peak plasma concentrations occur at one hour and plasma terminal half-life at two to six hours (King, Volpicelli, Gunduz, O'Brien, & Kreek, 1997).

The most common side-effect of Naltrexone at a 50-mg dose is nausea (Berg, Pettinati, & Volpicelli, 1996; Carmen et al., 2004). Other, less common, side effects of Naltrexone include vomiting, headache, light-headedness, anxiety, fatigue, skin tingling, stomach cramps, irritability, dizziness and nervousness (Farren et al., 1999). The incidence of nausea is more common in women and participants of a younger age (O’Malley, Krishnan-Sarin, Farren, & O’Connor, 2000). To combat the possibility of Naltrexone-induced nausea, participants were instructed to take their dose with a meal (Rohsenow et al., 2000).

Depression has also been reported as an adverse effect as Naltrexone blocks the positive effects associated with opioid peptides. However, there is conflicting evidence as to whether depression or dysphoria are clinically important adverse effects of Naltrexone. Mendelson, Ellingboe, Keuhnle, and Mello (1978) administered a single dose of 50-mg of Naltrexone to seven healthy adult males, with no history of opiate abuse. All subjects reported that Naltrexone produced dysphoric effects. Since then, other studies have also described depression or dysphoria as a side effect of Naltrexone in healthy volunteers (Hollister, Johnson, Boukhabza, & Gillespie, 1981) or opioid-free former addicts (Crowley, Wagner, Zerbe, & MacDonald, 1985). On the other hand, Dean et al. (2006) administered 50-mg of Naltrexone to subjects with opioid dependence for a period of one year and reported that depression was not a common adverse effect of Naltrexone treatment. A review published by Miotto, McCann, Basch, and Ling (2002) on the use of Naltrexone in alcohol, opioid, and
nicotine studies, concluded that dysphoria was not a serious side effect of Naltrexone. Participants took their Naltrexone one hour prior to their experimental sessions.

**Opioid agonist.** MST Continus (morphini sulfas pentahydricus), a type of slow-release morphine, was used in this study. Morphine is primarily a µ-opioid receptor agonist, and to a lesser degree δ- and κ-receptors. It is metabolized into several metabolites; the major metabolic pathway of morphine includes the formation of morphine-3-glucuronide and morphine-6-glucuronide (M6G). The analgesic property of M6G is achieved through direct interaction with opioid receptors; M6G has a high affinity for µ1-opioid receptors (Janicki, 1997). Slow-release morphine tablets reach peak concentration in three hours and are sustained for 12 hours (Yang, 2002). Participants were instructed to take MST Continus three hours prior to their experimental session.

Variable dosages of MST Continus have been used in clinical studies involving healthy volunteers: 20-mg (Leslie, Rhodes, & Black, 1980), 30-mg (Westerling, Persson, & Höglund, 1995) and 90-mg (Bloomfield et al., 1993). Participants in the current study were administered 10-mg of MST Continus, a dose commonly given to healthy volunteers (Babul & Darke, 1993; Hoskin et al., 1989; Osborne, Joel, Trew, & Slevin, 1990).

As to the question of the effects of food on morphine absorption, the data for MST Continus is contradictory, with some studies reporting no difference in maximum drug plasma concentration (Cmax) and time to reach maximum drug plasma concentration (tmax) between the fed and fasted states (Kaiko et al., 1990), while others (Drake et al., 1996), report that food consumption does affect the rate and extent of morphine absorption. A review published by Collins, Faura, Moore, and McQuay (1998) concluded that there was no difference in Cmax and tmax between fed and fasted healthy volunteers. In other words, there was bioequivalence under the fed and fasted conditions. Participants were thus encouraged to take their medication with food.
Commonly reported side effects of morphine include nausea, emesis, dizziness, pallor, diaphoresis, headache, pruritus and fainting. Other effects such as sleepiness, euphoria, dry mouth, vision disturbance, relaxation and dizziness have also been reported (Pud et al., 2006) At a dose of 90-mg of MST Continus, specific adverse effects that have been reported are somnolence, dizziness, dry mouth, pruritus, asthenia or headache, and nausea (Bloomfield et al., 1993). A concern in the current study was the sedating effects that Morphine could have on the cognitive demands of the behavioural tasks participants were expected to complete. Although opioids as a class of drugs generally do not significantly impair cognitive and psychomotor performance (Zacny, 1995), reported findings in the literature are highly variable. Some studies report impairments on memory tasks. Cleeland et al. (1996) found long term memory deficits in healthy volunteers on a 30mg dose of oral morphine. Kamboj, Tookman, Jones, and Curran (2005) found both an anterograde and retrograde aspect to memory impairments following morphine. However, subjects in this study were palliative care patients receiving chronic oral morphine. In contrast, and of relevance to this study as identical doses were used, Friswell et al. (2008) looked at the memory performance of healthy volunteers on 10-mg of morphine and found no significant effects on anterograde and retrograde memory performance. Similarly, Walker and Zacny (1998) found that doses of 40-mg of morphine did not produce significant psychomotor and cognitive deficits, including memory. Even on doses as high as 45-mg, no deficits on tasks measuring reaction time, eye-hand coordination, logical reasoning and short-term memory have been reported (Hanks, O Neill, Simpson, & Wesnes, 1995). Sex hormones may have a modest influence on opioid responses (Ribeiro-Dasilva et al., 2011; Zacny, 2001). Women of reproductive age have higher μ-opioid receptor binding values than men (Zubieta et al., 1999). Reports on sex differences with respect to adverse effects are variable. Some studies report that women experience a significantly greater number of side effects than men, such as
nausea and emesis (Fillingim et al., 2005) and feeling “spaced out”, “sluggish” and “dry mouth” (Zacny, 2001). Others, like Gupta et al. (2014) found that sex differences did not significantly affect the likelihood of experiencing side effects with morphine.

**Dopamine agonist.** As exogenous DA cannot cross the blood-brain barrier, the physiological precursor, Levodopa (L-DOPA), was administered. Once it crosses the hemato-meningeal barrier, L-DOPA is transformed into DA by dopa-decarboxylase. Madopar is the trade name for L-DOPA used in this study. Madopar contains L-DOPA (200-mg) and Benserazide (50-mg). L-DOPA acts on both D1 and D2 receptors (Schapira et al., 2006). Benserazide is a peripheral inhibitor of DOPA decarboxylase that prevents DOPA from being metabolized to DA in the blood (Rihet, Possama, Micallef-Roll, Blin, & Hasbroucq, 2002). The dose of 200-mg L-DOPA and 50-mg benserazide used in this study has been shown to have significant behavioural effects in healthy subjects (Hitz et al., 2012; Keller et al., 2011; Micallef-Roll, Rihet, Hasbroucq, Possamai, & Blin, 2001; Rihet et al., 2002). The experimental sessions started 60 minutes after oral intake of Madopar - a time that has been demonstrated to reflect peak plasma concentrations of the drug (Eisenegger et al., 2010; Flöel et al., 2005).

Common side effects of L-DOPA are drowsiness and nausea (Koller, Hutton, Tolosa, & Capilldeo, 1999; Rihet et al., 2002), vomiting, dizziness, fatigue (Buhmann et al., 2003; Liggins, Pihl, Benkelfat, & Leyton, 2012) and dyskinesia (Koller et al., 1999). Side-effects in healthy volunteers on doses of Madopar identical to the ones used in the current study are mild tiredness, headache (Gasser, Crevoisier, Ouwerkerk, Lankhaar, & Dingemanse, 1998) and nausea (Gasser et al., 1998; Haslinger et al., 2001).

Once again, reports on the effects of food consumption on L-DOPA are variable and illustrate the unpredictability of drug-food interactions (Gillespie, Mena, Cotzias, & Bell, 1973). High protein meals have been shown to have a negative impact on the clinical
response to levodopa in Parkinson’s patients (Tsui et al., 1989). On the other hand, it has also been shown that there is poor bioavailability of L-DOPA following low-protein meals when compared to fasting (Robertson et al., 1991). Other studies have described reduced absorption following a standard meal in Parkinson patients (Roos, Tijssen, Van der Velde, & Breimer, 1993) and increased absorption following a light breakfast in healthy volunteers (Wilding et al., 1991). Crevoisier, Zerr, Calvi-Gries, and Nilssend (2003) reported that although food decreased the rate of L-DOPA absorption, it had no effect on the systemic exposure to levodopa. Similar results have previously been reported by Robertson et al. (1991) who found that initial peak and maximum plasma drug concentrations of L-DOPA were not affected by food. In the present study, participants were not dissuaded from consuming a meal with their medication—a practice followed in several studies examining various aspects of levodopa in healthy volunteers (Barthelmebs, Mbou, Stephan, Grima, & Imbs, 1993; Linssen, Sambeth, Vuurman, & Riedel, 2014; Morris, Parsons, Trounce, & Groves, 1976). The main purpose of allowing food consumption with the medication was to minimize the side effect of vomiting.

**Dopamine antagonist.** Haloperidol (Sandoz Haloperidol), is a prototypic butyrophenone antipsychotic with a high affinity to D2 receptors. It is extensively metabolized in humans and this could account for the large individual variability in its pharmacokinetics (Kudo & Ishizaki, 1999). The average Tmax reported shows a wide variance among studies, from 1.7 to 6.1 hours (Kudo & Ishizaki, 1999; Lim et al., 2013). Participants in the current study were assessed three hours after drug administration. A dose of 5-mg of Haloperidol was administered in the present study—a dose commonly given to healthy subjects (Gasso et al., 2013; King, Burke, & Lucas, 1995; Mas et al., 2013; Midha et al., 1989; Saeedi, Remington, & Christensen, 2006; Vernaleken et al., 2006).

Frequently reported adverse effects after Haloperidol administration are sedation/sleepiness (Anderson, Reker, & Cooper, 1981; King et al., 1995; Liem-Moolenaar et
al., 2010), dysphoria, agitation and akathisia (Anderson et al., 1981; King et al., 1995). There is considerable evidence linking the level of D2 occupancy with extrapyramidal symptoms (EPS), with the risk of EPS rising with D2 blockade of 80% (approximately 5-mg of Haloperidol) or higher (Kapur, Zipursky, Jones, Remington, & Houle, 2000). Furthermore, adverse effects in the domains of both affect and cognition can occur with D2 receptor occupancy in excess of approximately 70%-80% (between 3- to 5-mg) in healthy subjects: sustained attention (Saeedi et al., 2006; Vernaleken et al., 2006; Veselinovic et al., 2013), reaction time and impaired processing speed (Saeedi et al., 2006; Veselinovic et al., 2013). For affect, the most notable changes have been seen on measures of contentment, confusion, anger (Saeedi et al., 2006) and avolition, apathy (Mas et al., 2013), and decreased interest in surroundings and commitments (Veselinovic et al., 2013). A single dose of 5-mg Haloperidol has also been shown to produce negative symptoms in normal individuals, but it was argued that drowsiness was an important confounding factor in the assessment of negative symptoms (Artaloytia et al., 2006). Haloperidol can be consumed with or without food (McKim, 2007).

**Placebo.** Folic acid (also known as folate) was used as the placebo substance for this study. A dosage of 5-mg was given to the participants. This placebo was taken one hour prior to the psychoanalytic sessions. Folic acid is a B vitamin.

**Antiemetic.** Medication in the form of 50-mg of Adco-Cyclizine was provided to all the participants in this study. This was a precautionary measure in the event any participant experienced any nausea or vomiting while on any of the above-mentioned substances. Adco-Cyclizine is typically used to treat and prevent motion sickness. It is classed as an antihistamine (histamine antagonist) drug.
**Statistical Analyses**

**Scoring the measures and deriving outcome variables.** As previously mentioned, the hypotheses of this study were investigated using both quantitative and qualitative approached. The *quantitative* approach refers to the use of psychometric measures completed by participants at both baseline and after each medication. The following sub-scales were used in the psychometric measures analyses and scored using standard procedures outlined in the relevant scoring manuals:

1. SEEKING and PANIC/GRIEF sub-scales of the ANPS.
2. PA and NA sub-scales of the PANAS,
3. MDI (specifically, the rating of the severity of depression scores),
4. Anxiety, Avoidance, and Security sub-scales of the SAAM,
5. Avoidance and Anxiety sub-scales of the ECR-(R).

The *qualitative* approach refers to the use of informal psychological probes such as ‘free associations’, ‘directed probes’ and recalling of ‘memories of loss’. This data was obtained during the psychodynamic interviews following each medication, and was comparatively more descriptive in nature, compared to the data obtained from the psychometric measures. Obtaining this kind of data was crucial as the psychological phenomena under investigation in this study were subtle and complex. Relying solely on crude psychometric measures would not have been sufficient as it was imperative to gain an understanding of the various phenomena from the perspective of the individual experience. Statistical and content analyses were performed on this data.

‘*Free-association*’ refers to the part of the interview where participants were asked to describe in their own words how they felt after taking a particular medication.

‘*Directed probes*’ refers to the part of the interview where participants were asked to qualitatively describe and then quantify/rate the change (from baseline) they experienced in
SEEKING and PANIC/GRIEF as a result of the medication taken. Participants had to rate, on a scale from 0 (no change) to 3 (the highest possible change) the change in increased SEEKING and decreased SEEKING. These scores were then subtracted to give an overall change in SEEKING. For example, if a participant rated the change in increased SEEKING as 0 (i.e., no change) and the change in decreased SEEKING as 1 (i.e., a mild change) then their overall change would be -1 (indicating an overall decrease in SEEKING). These scores were then categorised as follows: -1 (a decrease in SEEKING), 0 (no change in SEEKING), 1 (increase in SEEKING). The aim was to compare whether the changes in SEEKING (decrease, no change or increase) were associated with the use of the dopamine agonist vs antagonist. The same method was used to quantify the change in PANIC/GRIEF, and the aim was to compare whether the changes in PANIC/GRIEF (decrease, no change or increase) were associated with the use of the opioid agonist vs antagonist. Fischer Exact Test analyses were performed on this data. Furthermore, Spearman’s Correlations were also run to see if there were any associations between the ‘directed probes’ and their psychometric counterpart (ANPS).

‘Memories of loss’ refers to the part of the interview where participants were asked to recall their three memories of loss and then to describe and quantify the change in overall emotional intensity for each memory compared to baseline. Change in emotional intensity was rated on a scale of 0 (no change) to 3 (the highest possible change in intensity) for each memory, and the scores summed to provide an overall change in emotional intensity score. Therefore, the overall score could range from 0 to 9. The overall scores were then categorised as follows: 0 = category 0 [no emotional intensity change]; 1-3 = category 1 [mild emotional intensity change]; 4-6 = category 2 [moderate emotional intensity change] and 7-9 = category 3 [extreme emotional intensity change]. The aim was to compare these counts between each
of the medications to establish if there was an association between medication type and emotional intensity change. Fischer Exact Test analyses were performed on this data.

As previously mentioned, a conventional content analysis of all the psychological probes data was undertaken. The purpose of a conventional content analysis is to describe a phenomenon (Hsieh & Shannon, 2005), which in this study was the affective responses of participants to the medications. This approach was chosen for three reasons. Firstly, it is suitable for exploratory research as it allows for the reporting of common issues in the data (Green & Thorogood, 2004), secondly, data can be quantified (i.e. number of counts) or weighted (Gbrich, 2007) and thirdly, the approach to coding of the data is more descriptive than interpretive (Morgan, 1993).

**Power analysis.** For the whole sample analysis, an a priori power analysis suggested that the sample size be set at \( N = 47 \) to achieve a statistical power > .90 using a Wilcoxon signed-rank test for matched pairs given a medium effect size. However, only 16 participants completed the current study. This sample size generated statistical power of .59.

For the split-sample analysis, a power analysis suggested that the sample size be set at \( N = 106 \) (\( n = 53 \) per group) to achieve a statistical power > .80 using a Mann-Whitney \( U \) test for independent between-group analyses given a medium effect size. However, only 16 participants were enrolled in the current study \( (N = 8 \) per group). This sample size generated statistical power of .24. The small sample size of the current study is a serious limitation and is discussed in detail under the limitations section.

**Inferential statistical analyses.** All analyses were conducted using SPSS version 23 and R (the *Exact* package). Due to the number of individual tests run, inflated Type 1 familywise error was an issue. However, correcting the \( p \)-value would have resulted in a significance value that was too stringent, especially considering that the research was exploratory, the analyses preliminary and the sample size small. It was considered more
important to try and establish what differences may exist for potential follow up studies. For this reason, the significance value was kept at .05 for all the analyses, with the knowledge that some of the significant results may be false-positives. For each of the analyses described below, the appropriate effect size estimate was calculated, and interpreted following convention. Cohen’s (1988) guidelines for r for Wilcoxon nonparametric tests (using the z value to calculate effect size) are: large effect is .5, medium effect is .3, and a small effect is .1. For Cramer’s V, a small effect is 0.1, a medium effect is 0.3 and a large effect is 0.5. All inferential statistical tests were non-parametric given the small sample size and the data was not normally distributed.

For the *psychometric measures*, the analyses proceeded across three stages. First, a series of Wilcoxon signed-rank tests (non-parametric test for related samples) were used to analyse differences in the five outcome variables (SEEKING, PANIC/GRIEF, PA, NA and MDI) as a function of medication for the whole sample. These analyses aimed to investigate differences on these specific measures between pre-medications (i.e., baseline) and post-medications. Specifically, these analyses assessed: (1) the effect of the DA agonist (Madopar) on SEEKING, PA and MDI; (2) the effect of the DA antagonist (Haloperidol) on SEEKING, NA and MDI; (3) the effect of the opioid agonist (Morphine) on PANIC/GRIEF, PA and MDI and (4) the effect of the opioid antagonist (Naltrexone) on PANIC/GRIEF, NA and MDI. All these analyses were directional (one-tailed) and undertaken in relation to hypotheses one to four.

The attachment measure SAAM was not administered at baseline and could therefore not be included in the aforementioned analysis. To investigate medication effects on the SAAM specifically, a series of Wilcoxon signed-rank tests analysed the relative effects of the opioid medications on the three SAAM sub-scales. Participant’s scores on each of the three sub-scales were compared post-opioid agonist versus post-opioid antagonist. Only the opioid
based medications were investigated considering the prominent role that opioids play in mediating social bonds.

The specific constructs of ‘despair’ and ‘protest’ were then investigated separately. The ‘despair’ construct was investigated by splitting the sample into two groups according to MDI-baseline scores, with one group comprising the lower set of scores and the other the higher set of scores. The High and Low depression groups therefore represented high and low ‘despair’ respectively. Prior to the split, the baseline range of scores for the entire sample on the MDI was 2-15, indicating that depression was not present in the sample. Naturally, after the split, the means for the High-MDI ($M = 11.00$) and Low-MDI ($M = 5.50$) groups remained within the ‘no or doubtful depression’ range. The prediction was that those with higher MDI-baseline scores (i.e., high ‘despair’ group) would respond differently to the medications compared to those with lower MDI-baseline scores (i.e., low ‘despair’ group). A series of Mann-Whitney U tests were used to assess the magnitude of change (from baseline to medication) between the Low- and High-MDI groups by comparing their scores on the five outcome variables. These analyses were non-directional (i.e., two-tailed) and were undertaken in relation to hypothesis five.

The sample was again split into two groups according to ECR-Avoidance and Anxiety baseline scores, with one group comprising the lower set of scores and the other the higher set of scores. This analysis was conducted as attachment is central to the study’s central hypothesis that depression may be an abnormal variant of the normal mammalian separation response. The High and Low Avoidance and Anxiety groups thus represented high and low ‘protest’ respectively. Prior to the split, the baseline median score for ECR-anxiety was 5.47, and for ECR-avoidance was 5.64. The prediction was that those with higher baseline avoidant/anxiety scores (i.e., high ‘protest’) would respond differently to the medications than those with lower baseline avoidance/anxiety scores (i.e., low ‘protest’). A series of
Mann-Whitney U tests were used to assess the magnitude of change (from baseline to treatment) between the Low- and High-ECR groups by comparing their scores on the five outcome variables. These analyses were non-directional (i.e., two-tailed) and were undertaken in relation to hypothesis six.

As previously mentioned, statistical analyses were also carried out on some of the psychological probes data. The analyses proceeded across three stages. First, in relation to the ‘directed probes’, a series of Fisher’s Exact tests (because > than 20% of observed counts were less than 5) assessed whether self-reported changes in SEEKING were associated with the DA medications, and whether self-reported changes in PANIC/GRIEF were associated with the opioid medications. Second, in relation to the ‘memories of loss’, a Fisher’s exact test assessed whether there was an association between change in emotional intensity for the re-experiencing of the three memories of emotional loss and the different medications. All the Fischer’s analyses for the psychological probes were directional (i.e., one-tailed) for the whole sample analyses but non-directional (i.e., two-tailed) for the split-sample analyses. Lastly, and in relation to the ‘directed probes’, a series of Spearman’s Rank-Order correlation analyses assessed whether self-reported changes in SEEKING and PANIC/GRIEF were associated with psychometric changes in SEEKING and PANIC/GRIEF (this change was calculated as the difference in SEEKING and PANIC/GRIEF scores on the ANPS from baseline to medication). The psychometric changes in SEEKING and PANIC/GRIEF were then coded to match the coding of the directed probes as follows: -1 (a decrease), 0 (no change), and 1 (an increase). All the correlation analyses were performed on the sets of coded data, and all were directional (i.e., one-tailed).

**Content analysis of psychological probes data.** Transcripts of the psychological probes data, which included ‘free associations’, ‘directed probes’ and recalling of ‘memories of loss’, were given to two independent coders (coders A), who were provided with a brief
rationale of the study, but who were not aware of the study’s hypotheses. The coders conducted their initial analysis of the transcripts independently. They each began with a type of “in vivo” coding exercise (Smith & Davies, 2010) searching for words or phrases in the transcripts that stood out and using the participant’s exact words/phrase as a code. This was followed by a more focused coding exercise which entailed identifying the most frequent codes and developing prominent categories of affective responses, as described in Saldaña (2013). Each category was then weighted as ‘x/16 participants had this similar affective response to this particular medication’. The various categories were then ordered according to their respective weighting. Thereafter, the two coders met to compare their respective analyses and to agree on the most frequently occurring affective categories for each medication. A final list of 13 categories of affective responses was compiled, with each category being assigned a descriptor code depicting words or phrases used by participants. Of the 13, seven affective responses on the list were regarded as prominent because these affects were identified in at least half of the participants on a particular medication (they were: positively stimulated, negatively stimulated, lowered drive, relaxed, detached, muted pain/detachment and connected). The balance of affective responses were regarded as less prominent because these affects were only identified in less than half of the participants (they were: happy, longing, compassion, acceptance, irritation/agitation and overwhelmed).

The list of affective categories (without any reference to medication type) was then given to a further two independent coders (coders B). Coders B were instructed to identify which of the affects on the list, if any, were experienced by each participant. The purpose of this was to establish whether they could identify the same participants that coders A had originally identified who were experiencing a particular affect. These coders were unfamiliar with the study’s rationale and hypotheses.
CHAPTER FOUR:

Results

Results are reported in the following order:

- For the whole sample I report (1) physical side-effects of the medications, (2) psychobehavioural effects of the medications, (3) psychoanalyst’s ratings, (4) baseline descriptives prior to medication, (5) descriptives of the psychometric measures across medications, (6) psychological probes data: coding, ‘directed probes’, ‘memories of loss’ and (7) testing hypotheses 1 to 4.

- For the split MDI sample, I report (1) psychobehavioural effects of the medications, (2) baseline descriptives prior to medication, (3) descriptives of the psychometric measures across medications, and (4) testing hypothesis 5.

- For the split ECR-Avoidance/Anxiety samples I report, (1) psychobehavioural effects of the medications, (2) baseline descriptives prior to medication, (3) descriptives of the psychometric measures across medications, and (4) testing hypothesis 6

Results of Psychometric and Psychological Probes Data Analyses for the Whole Sample

Physical side-effects of the medications. Table 1 reports the number of participants that experienced each side-effect. The most severe side-effect was akathisia which four participants experienced on Haloperidol. Physical side-effects were reported least commonly with Placebo and Morphine and most often with Madopar, Haloperidol and Naltrexone (most commonly, elevated heart rate, feeling fuzzy/foggy, tiredness, and feeling jittery/shaky).
Table 1

*Physical Side-effects to the Medications*

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Madopar</th>
<th>Haloperidol</th>
<th>Morphine</th>
<th>Naltrexone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated heart rate</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Jittery/Shaky/Buzzy</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Fuzzy/Foggy</td>
<td>3</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>2</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiredness</td>
<td>1</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Restlessness</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akathisia</td>
<td></td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>11</td>
</tr>
</tbody>
</table>

Subjective psychobehavioural effects of medications. Table 2 reports the number of participants that experienced each of the listed subjective changes in psychobehavioural state. The descriptors listed were used by the participants themselves. Positive effects were experienced with Madopar and Morphine more commonly than with Haloperidol, Naltrexone and Placebo. Although negative effects were experienced for all the medications, they were more commonly experienced with Haloperidol, Madopar and Naltrexone.
<table>
<thead>
<tr>
<th>Type of effect</th>
<th>Madopar</th>
<th>Haloperidol</th>
<th>Morphine</th>
<th>Naltrexone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safe/Secure</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Comfortable</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hopeful</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Optimistic</td>
<td>2</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Confident</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Engaged</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Happy</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Positive</td>
<td>3</td>
<td></td>
<td></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Upbeat</td>
<td>3</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nice</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Curious</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Calm</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Talkative</td>
<td>3</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Relaxed</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Euphoric</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Need for closeness</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Warm</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Attached</td>
<td>2</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Content</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Less concerned</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Humorous</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Stimulated</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
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</tr>
<tr>
<td>Connected</td>
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<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Disinhibited</td>
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<td>Enthusiastic</td>
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<td></td>
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<tr>
<td>Accepting</td>
<td>1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Alert</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Energetic</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
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<tr>
<td>Negative</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Subdued</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>3</td>
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<td>Sad</td>
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<td>1</td>
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<td>Anxious</td>
<td>7</td>
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<td>1</td>
<td>3</td>
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<tr>
<td>Rushed</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Difficulty Concentrating</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Withdrawn</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Angry</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
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<tr>
<td>Separated/Detached/Disconnected</td>
<td>6</td>
<td>8</td>
<td>7</td>
<td>8</td>
<td>4</td>
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<td>Less Happy</td>
<td>3</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Reluctant to engage</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
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<td>Less secure</td>
<td>1</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lonely</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Isolated</td>
<td>2</td>
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<td></td>
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<tr>
<td>Panicky</td>
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<td>3</td>
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<td>Apathetic</td>
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<td>Less excited</td>
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<td>Indifferent</td>
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<td>3</td>
<td>4</td>
<td>5</td>
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<td>---</td>
</tr>
<tr>
<td>Irritable</td>
<td></td>
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<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less motivated</td>
<td>3</td>
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<td>2</td>
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<td></td>
</tr>
<tr>
<td>Less interested</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Despondent</td>
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<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hopeless</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

**Psychoanalyst’s ratings.** As previously mentioned, the psychoanalyst was required to make a prediction as to what medication he thought each participant had taken after each experimental session. The success of his predictions was as follows: 50% in the case of Morphine, 6.25% in the case of Naltrexone, 18.75% in the case of Madopar, 25% in the case of Haloperidol and 43.75% for Placebo. Six participants spontaneously and correctly identified when they had been given Placebo.\(^1\)

**Baseline descriptives prior to medication.** Table 3 shows the means, standard deviations, and ranges of all four psychometric measures completed prior to medication.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Baseline Descriptive Statistics for Psychometric Measures for the Whole Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEEKING</td>
</tr>
<tr>
<td>Mean</td>
<td>30.63</td>
</tr>
<tr>
<td>SD</td>
<td>3.93</td>
</tr>
<tr>
<td>Range</td>
<td>25 - 39</td>
</tr>
</tbody>
</table>

*Note. SEEKING = ANPS seeking sub-scale; PANIC/GRIEF = ANPS panic/grief subscale; PA = PANAS positive sub-scale; NA = PANAS negative sub-scale; E_Anx = ECR attachment-related anxiety sub-scale; E_Av = ECR attachment-related avoidance sub-scale; MDI = total severity of depression score.*

The mean for SEEKING was 30.63 (*SD* = 3.93) and the mean for PANIC/GRIEF was 21.83 (*SD* = 4.67). Davis et al. (2003) provided norms for the ANPS derived from two population groups, undergraduate students (*N* = 171; \(M_{\text{age}} = 20.3\pm3.5\) years) and job applicants (*N* = 598; \(M_{\text{age}} = 41.9\pm10.3\) years). I chose to compare sample means with the job applicant population rather than the student population group since the mean age of the

\(^{1}\) If there is any doubt that Placebo could be identified by participants by the absence of side-effects is covered by the fact that 5 of the 16 participants experienced side effects on Placebo.
former was relatively closer to the mean age of the current sample ($M_{age} = 35$). Unfortunately, the norms provided by Davis and colleagues were not for the entire sample but were reported
for each gender (SEEKING $M$ for males = 28.07, SEEKING $M$ for females = 28.52; PANIC/GRIEF $M$ for males = 15.58, PANIC/GRIEF $M$ for females = 16.52). The current sample was too small to separate out gender effects, but the sample means for SEEKING and PANIC/GRIEF were in keeping with the means for both genders. The means for PA and NA were 34.19 ($SD = 4.79$) and 13.19 ($SD = 2.71$) respectively. According to Watson et al., (1988), the normal population will have a mean PA score of 29.7 ($SD = 7.9$) and a mean NA score of 14.8 ($SD = 5.4$). Current sample means conformed to these suggested norms. The mean ‘severity of depression’ score for the current sample was 8.25 which fell within the ‘no or doubtful depression’ range (a score between 0 and 20) of the MDI (Bech et al., 2015). The means for avoidance and anxiety on the ECR-R were 5.59 ($SD = 0.94$) and 5.40 ($SD = 0.80$) respectively. The ECR-R is generally utilised with continuous data and there are as such no standardised norms (personal communication; Fraley, 2015). However, some norms were provided by Fraley (2015) based on a sample of 17 000 ($M_{age} = 27 \pm 10$ years). The mean for the avoidance and anxiety ECR subscales were 2.92 ($SD = 1.19$) and 3.56 ($SD = 1.12$) respectively (Fraley, 2012). Current sample means were comparatively higher. Single sample t-tests (non-directional) showed that the mean difference for ECR-avoidance between the current sample and the published means (mean difference = 2.67) was significant, $t(15) = 11.31, p < .001$, as was the mean difference for ECR-anxiety between the current sample and the published means (mean difference = 1.83), $t(15) = 9.20, p < .001$.

In summary, the descriptive data at baseline showed that the current sample was not clinically depressed, did not display higher than normal PA or NA, and both SEEKING, and PANIC/GRIEF were in keeping with published norms. With regards to the ECR, it would appear that the current sample was more avoidant and anxious compared to available norms. This claim however is made with reservation as the current sample and the normed sample
were not entirely comparable. For example, the mean age of the normed sample was $M_{\text{age}} = 27 \pm 10$ years, compared to the mean age of the current sample of $M_{\text{age}} = 35 \pm 11.84$ years.

**Descriptives for psychometric measures following medication.** Table 4 presents the means, standard deviations, and ranges for each of the psychometric measures as a function of medication. PA was decreased from baseline ($M = 34.19$) and NA was decreased from baseline ($M = 13.19$) on all medications except for Madopar ($M = 15.81$), where NA increased from baseline. MDI scores increased from baseline ($M = 8.25$) on all medications, except for Placebo ($M = 7.31$), where depression scores decreased from baseline. Despite this increase, the means for all the MDI scores on the different medications remained within the ‘no depression’ range (that is, below 20). On the ANPS, the means for SEEKING and PANIC/GRIEF decreased from baseline ($M = 30.63$ and $21.28$ respectively) across all medications. The SAAM (a state measure) was not administered at baseline, thus no baseline means were available for comparison.
Table 4  
Scores on Psychometric Measures as a Function of Medication for the Whole Sample

<table>
<thead>
<tr>
<th>Medication</th>
<th>SEEKING</th>
<th>PANIC/GRIEF</th>
<th>PA</th>
<th>NA</th>
<th>MDI</th>
<th>S_Anx</th>
<th>S_Av</th>
<th>S_Sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>21.63 (5.41)</td>
<td>17.44 (0.70)</td>
<td>23.81 (7.92)</td>
<td>11.88 (2.53)</td>
<td>9.19 (8.19)</td>
<td>3.44 (0.95)</td>
<td>2.53 (0.32)</td>
<td>5.55 (0.98)</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>20.19 (6.33)</td>
<td>19.50 (2.19)</td>
<td>21.69 (8.42)</td>
<td>12.75 (3.12)</td>
<td>12.06 (9.46)</td>
<td>3.60 (0.87)</td>
<td>3.15 (1.26)</td>
<td>5.30 (1.07)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>22.69 (8.00)</td>
<td>18.81 (3.41)</td>
<td>25.88 (8.68)</td>
<td>12.25 (3.44)</td>
<td>11.50 (9.78)</td>
<td>3.74 (1.04)</td>
<td>2.23 (1.21)</td>
<td>5.88 (0.74)</td>
</tr>
<tr>
<td></td>
<td>5 – 35</td>
<td>12 - 25</td>
<td>13 - 38</td>
<td>10 - 22</td>
<td>0 - 33</td>
<td>1.86 – 6.57</td>
<td>1.00 – 5.29</td>
<td>4.71 – 7.00</td>
</tr>
<tr>
<td>Madopar</td>
<td>21.94 (8.06)</td>
<td>19.88 (5.44)</td>
<td>28.13 (10.93)</td>
<td>15.81 (5.62)</td>
<td>12.06 (10.98)</td>
<td>3.54 (1.10)</td>
<td>2.81 (1.59)</td>
<td>5.41 (1.13)</td>
</tr>
<tr>
<td></td>
<td>6 – 31</td>
<td>11 - 30</td>
<td>11 - 47</td>
<td>10 - 28</td>
<td>0 - 32</td>
<td>2.14 – 6.00</td>
<td>1.00 – 5.57</td>
<td>3.14 – 7.00</td>
</tr>
<tr>
<td>Placebo</td>
<td>23.31 (6.01)</td>
<td>18.19 (3.75)</td>
<td>30.75 (8.55)</td>
<td>12.50 (2.83)</td>
<td>7.31 (8.35)</td>
<td>3.70 (0.73)</td>
<td>2.18 (1.03)</td>
<td>5.90 (0.56)</td>
</tr>
</tbody>
</table>

Note. On the first row of each medication condition, means are presented with standard deviations in parentheses, and on the second row, the range of scores. SEEKING = ANPS seeking sub-scale; PANIC/GRIEF = ANPS panic/grief subscale; PA = PANAS positive sub-scale; NA= PANAS negative sub-scale; MDI = total severity of depression score; S_Anx = SAAM anxiety sub-scale; S_Av = SAAM avoidance sub-scale; S_Sec = SAAM security sub-scale.
Psychological probes data.

**Coding.** As previously mentioned, coders A identified a total of 13 affective responses across the five medications in the psychological probes data (‘free associations’, ‘directed probes’ and ‘memories of loss’). The first seven were considered prominent as they were identified in at least 50% of participants. They were:

1. Feeling positively stimulated. Many participants had some form of physiological reaction (such as elevated heartrate, jittery, fidgety, shaky, rush of adrenaline, butterflies in my tummy) to all the medications but especially Madopar. Half of the participants felt stimulated by these physiological reactions and interpreted these reactions in a positive manner. They reported feeling happy, excited, upbeat, engaged, secure or confident.

2. Feeling negatively stimulated. Other participants however did not respond well to the physiological reactions and felt quite distressed by them. They reported feeling anxious, restless, detached, had difficulty concentrating and were reluctant to engage. This was seen on Naltrexone and Haloperidol, but especially Madopar.

3. Low drive. Almost all participants experienced a physiological and mental ‘slowing down’, to varying degrees, on one or more of the medications but especially on Haloperidol and Naltrexone. This reduction in drive was characterised by a loss of energy, interest, motivation or wanting to withdraw.

4. Relaxed. Many participants reported that some of the medications made them feel quite relaxed, especially Morphine and Haloperidol. There was a clear absence of negative affect and a sense of well-being. Relaxation in this context was characterised by descriptions of feeling comfortable, calm, at ease, mellow, content or secure.
5. Detached. A very common affect, especially on Haloperidol, Naltrexone and Morphine, were feelings of detachment (or separation, disconnection and indifference), which were particularly evident when participants were recalling their memories of loss, and related to feeling distanced from their emotions, the actual memory or from other people.

6. Muted pain/detachment. There was a close overlap between this affect and the one above in the sense that in both instances participants expressed feeling distanced from their memories. However, in the case of feeling a ‘muted sense of pain/detachment’, participants felt removed not only from the memory itself but specifically referred to feeling removed or distanced from the sadness and pain associated with their memories. This was seen on Madopar and Haloperidol, but especially Morphine.

7. Connected. This referred to participant’s sense of interpersonal connection with others or a connection to positive images of the individuals in their memories. With regards to lost loved ones, the connection that they used to have was foregrounded and looked upon with fond remembrance. Some participants also regarded their connection with loved ones as less damaged as they previously thought. This was particularly common on Morphine.

Less prominent were:

8. Happy. This particular affect closely missed being classified as prominent. It featured quite strongly in Morphine and Madopar. It was not merely the absence of negative feelings but referred to a sense of hope, optimism and positivity.
9. Longing. A few participants expressed a desire or longing for closeness or contact with loved ones or felt lonely because they were really missing something or someone they had lost. This affect was mostly identified on Haloperidol, Naltrexone and Morphine.

10. Compassion. Participants expressed sympathy for or a greater understanding of the actions of persons who had caused them pain in the past, but more often the sympathy was directed towards themselves. Reflecting on the nature of and the reaction to their loss, some participants reported that they felt sorry for the person they were then and that they felt less critical about themselves now. This was seen especially on Madopar.

11. Acceptance. Some participants described feeling a sort of coming to terms with or acceptance of their loss. They were able to rationalise and think through their loss in a less emotive manner and in some cases consider it resolved. Interestingly, this affect was relatively common on Placebo.

12. Irritation/Agitation. There were several participants who felt particularly irritated or agitated either with friends or the people in their memories, but more often, they simply felt agitated at being at the session and could not relax and expressed a desire to distract themselves from their current situation. This was evident across all medications except for Morphine.

13. Overwhelmed. There were several participants who felt panicky or out of control in relation to the somatic effects of the medications, especially Madopar. This affect is quite similar to feeling ‘negatively stimulated’, but in this case, the difference was that there was an added component of panic, which made patients feel overwhelmed.

There was complete agreement between coders A and B as to which affects
featured prominently (1-7) and which did not feature prominently (8-13).

‘Directed probes’. These refer to participant’s self-reported changes during the ‘directed probes’ part of the interview, when they were asked whether or not they had experienced any change in SEEKING and PANIC/GRIEF after each medication and if so, to qualify the degree of this change.

On Madopar, nine participants reported a mild to moderate increase in SEEKING. On Haloperidol, eight participants reported a mild to extreme decrease in SEEKING. Half of the participants reported a decrease in PANIC/GRIEF on Morphine, with the intensity of the change being equally allocated between mild and moderate. On Naltrexone, nine participants reported no change in PANIC/GRIEF. Lastly, on Placebo most participants reported no changes with respect to SEEKING and PANIC/GRIEF.

‘Memories of loss’. Participants were instructed prior to the experimental phase of the study to describe three autobiographical events associated with a significant personal loss. A total of 48 memories were recorded for the whole sample and allocated into the following categories: romantic disappointments (15), death of a parent, relative or friend (11), near-death of parent, relative or friend (4), death of a pet (4), parental divorce (2), relocating to another town or country (3), and existential loss, like loss of previous status (9). After participants recalled their three memories of loss on each medication, they had to describe and quantify the change in emotional intensity. These changes were then coded as either no change, mild, moderate and extreme changes in emotional intensity. To determine whether there was an association between type of medication and change in emotional intensity (from baseline), a Fischer’s Exact test compared the counts of the coded data across the various medications. The analysis detected a significant association between change in emotional intensity and drug trial type, $p = .035$, $V = .28$, in the whole sample, indicating that certain medications were more likely than others to result in a change in emotional intensity. To
explore this overall association further, a series of Fischer’s Exact Tests were again conducted to assess specific differences between medication types. Change in emotional intensity was significantly associated with each of the medications when compared to the Placebo trial (all $p s < .014$), except for Haloperidol, $p = .067$. When each medication was compared against the Placebo, change in emotional intensity was significantly greater when participants were taking the medications compared to the Placebo. There were no significant associations when each medication was compared with each another (all $p s > .340$), indicating that there were no significant differences in change in emotional intensity when participants were taking either the Dopamine or Opioid medications. Although participants were asked to rate the change in emotional intensity, they were unfortunately not specifically asked to rate whether this change meant that they re-experienced their loss with greater or lesser sadness/pain. This association could thus not be investigated statistically, only qualitatively. The breakdown of change in emotional intensity for ‘memories of loss’ across the five medications is shown in Table 5. Across all the medications, there were participants who reported no change in emotional intensity; the most being on Placebo. There was no dramatic difference between Madopar and Haloperidol with respect to the number of participants who reported ‘no change’, ‘mild change’, ‘moderate change’ and ‘extreme change’ in emotional intensity. Likewise, for Morphine versus Naltrexone. More participants reported a moderate change in emotional intensity on Morphine compared to the other medications and Madopar resulted in more extreme changes in emotional intensity compared to the other medications.
Table 5
Degree of Change in Emotional Intensity of Memories of Loss

<table>
<thead>
<tr>
<th></th>
<th>Madopar</th>
<th>Haloperidol</th>
<th>Morphine</th>
<th>Naltrexone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Mild change</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Moderate change</td>
<td>5</td>
<td>4</td>
<td>8</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Extreme change</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Testing hypothesis 1.** Madopar will significantly increase SEEKING and PA and significantly improve depressive mood, from baseline, on the quantitative measures. Madopar will also increase SEEKING and improve affective valence and mood as qualitatively described in the ‘directed probes’, ‘memories of loss’ and ‘free association’, paradigms.

A series of Wilcoxon tests were conducted to determine whether, compared to baseline, Madopar would significantly increase SEEKING and PA and significantly improve mood (see Table 6). The comparison for SEEKING on the ANPS was significant, $z = -3.35$, $p = .001$, but in the opposite direction to that predicted. Instead of increasing SEEKING as expected, Madopar reduced SEEKING in $N=14$. The comparison for PA was likewise significant, $z = -2.11$, $p = .018$, but once again, in the opposite direction to what was predicted. Instead of increasing PA, Madopar reduced PA in $N=11$. The comparison for mood on the MDI was not significant, $z = -0.60$, $p = .275$.

A series of Spearman’s Rank-Order correlation analyses were run to assess whether there was any association between the changes in SEEKING as measured by the psychometric ANPS and the changes in SEEKING as measured by the qualitative ‘directed probes’. The analyses detected no significant associations for Madopar ($r_s = .32$, $p = .112$), indicating that the psychometric and qualitative measures were not consistent with one another. On the psychometric ANPS, participants reported that Madopar generally reduced
SEEKING, whereas on the qualitative ‘directed probes’, they generally reported an increase in SEEKING (explaining why the analysis indicated no association).

On ‘memories of loss’, change in emotional intensity was significantly greater on Madopar, but only when compared to Placebo, and not to any of the other medications. Most participants reported some degree of change in emotional intensity on Madopar while re-experiencing their loss compared to only four who experienced no change. Qualitatively, of the 12 participants who reported a change, only two described an increase in sadness when re-experiencing their loss, as reflected in these statements “I feel the feelings stronger, stronger sadness and worried feelings” and “There’s sadness and feeling alone”. The other ten participant’s experience of recalling their loss was generally positive. There were some who experienced a decrease in the sadness and pain related to their memories, and others who felt distanced from the loss. These feelings are clearly depicted in the following examples: “The sadness is significantly less”, “Not as painful to think about it”, “Those feelings feel less intense now”, “I think the sense of loss is a bit more than normal, but not in a terrible way, just kind of a sad way, but more happy”, “I feel less of the self-esteem wound”, “I find it hard to even connect to that sadness”, “It seems less significant now”, “I’m much more able to hold contrasting feelings and think it through” and “It doesn’t evoke any negative emotions”.

A Fischer’s Exact test was used to compare changes in SEEKING on Madopar to changes in SEEKING on Haloperidol on the ‘directed probes’ specifically. There was a trend towards significance, $p = .061, V = .39$, with a medium effect size, for both dopamine medications. For Madopar, N=9 reported an increase in SEEKING, consistent with its predicted effects. For Haloperidol, N=8 reported a decrease in SEEKING, consistent with its predicted effects. These results indicate that participants qualitatively reported feeling increased SEEKING on Madopar and decreased SEEKING on Haloperidol.
On all the psychological probes data together, that is, ‘directed probes’, ‘memories of loss’ and ‘free association’, two prominent affects were identified by coders A for Madopar:

- Feeling positively stimulated: Several participants interpreted their physiological reactions to Madopar in a positive manner. Coders A identified this affect in eight participants. The following are examples of how these participants felt on Madopar: “I feel a buzz. A happy feeling”, “Slightly euphoric. Happy. I’m in a good mood”, “I’m moving from happiness to a more physiological activation. It’s not unpleasant”, “I actually feel quite good”, “I feel quite upbeat”, “It almost feels like a bit of a stimulant” and “I do feel optimistic though. I’m feeling pretty happy”. Some felt more confident, evident in examples like, “I do feel more confident. I do feel that with greater confidence, I could engage with social situations “or “I feel emotionally bold”. Other participants felt more connected or engaged, illustrated in the following examples “I feel I was more engaging, sort of feeling more excited about the connections that could possibly be made”, “I’m aware of feeling very safe here”, “I kind of feel like I could curl into a little ball and be taken care of” and “I feel upbeat. I feel engaged with everyone”. Some participants only experienced the expected effects of Madopar much later in the day, after they had left the session. One participant expressly felt disinhibited after leaving the interview session. She reported that she had “A little disinhibited engagement with Ross (the designated driver used in this study) in the car”. Another participant reported that after leaving the session she “I had the experience of meeting somebody and feeling instantly attracted to them”. And yet another participant’s description of how she felt later in the day is stereotypical of the effects of a dopamine agonist. She reported that “I felt unusually good. I felt on a high. I felt like I could run up on any mountain. I felt manic, very energetic”. Coders B identified this affect in the same eight participants coders A had originally identified. There was thus complete agreement between coders A and B.
Feeling negatively stimulated: The balance of participants interpreted their physiological reactions to Madopar in a negative manner. Coders A also identified this affect in eight participants. They felt anxious, evident in examples like “I feel very anxious. It feels as if someone is sitting on my chest”, “I’m more anxious…like stressing out quite a bit more than I think I normally would have” and “I’m definitely jittery and a bit anxious”. Others felt detached, evident in examples such as “The feelings are out of reach. Something else is overriding my feelings”, “It just feels as though I’m further away from it” or “I do feel a bit cut off from it though”. Some felt isolated and sad, illustrated in statements such as “I feel lonely. I feel left out”, “The lense that I’m looking at this memory through feels much more isolated”, “My sense of people’s attachment to me is more fragile right now. Easier to let me go and that feels quite sad”, “The thought of losing the people I love is much more distressing” and “I can feel a sense of longing. I do feel a sense of losing something that I want to have”. Coders B identified this affect in six of the eight participants originally identified by coders A. There was thus 75% agreement between coders A and B.

Based on the psychological probes data, it appears that Madopar did produce some effects more in keeping with predictions. Eight participants felt positively stimulated (both coders A and B were in complete agreement). Nine participants reported an increase in SEEKING on the ‘directed probes’ and 10 participants reflected on their ‘memories of loss’ in a more positive manner.

Testing hypothesis 2. Haloperidol will significantly decrease SEEKING, increase NA and significantly worsen depressive mood, from baseline, on the quantitative measures. Haloperidol will also decrease SEEKING and worsen affective valence and mood as qualitatively described in the ‘directed probes’, ‘memories of loss’ and ‘free association’, paradigms.
A series of Wilcoxon tests were conducted to determine whether, compared to baseline, Haloperidol would significantly decrease SEEKING, increase NA and significantly worsen mood (see Table 6). The comparison for SEEKING on the ANPS was significant, $z = -2.86, p = .002$, and in the direction predicted. Haloperidol reduced SEEKING in N=11.

According to Cohen’s guidelines, the effect size of this comparison was large. Haloperidol also reduced NA in N=11, but the comparison did not reach significance, $z = -1.52, p = .064$, and had no significant effect on mood, $z = -0.73, p = .235$, on the MDI.

Table 6

<table>
<thead>
<tr>
<th>Variable</th>
<th>$M$ Positive Ranks</th>
<th>$M$ Negative Ranks</th>
<th>$z$</th>
<th>$p$</th>
<th>$r$</th>
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<td></td>
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<td></td>
</tr>
<tr>
<td>SEEKING</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SEEKING</td>
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<td>.002</td>
<td>-0.51</td>
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<td>.064</td>
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<td>6.75</td>
<td>-0.73</td>
<td>.235</td>
<td>-0.13</td>
</tr>
</tbody>
</table>

Note. Dopamine Agonist = Madopar. Dopamine Antagonist = Haloperidol.

A series of Spearman’s Rank-Order correlation analyses were run to assess whether there was any association between the changes in SEEKING as measured by the psychometric ANPS and the changes in SEEKING as measured by the qualitative ‘directed probes’. The analyses detected a trend towards significance for Haloperidol ($r_s = .41, p = .059$). According to Cohen’s guidelines, the effect size of this comparison is medium, indicating some degree of association between the psychometric and qualitative measures. This is reasonable given that 11 participants reported a decrease in SEEKING on the ANPS and eight reported a decrease on the ‘directed probes’.

On ‘memories of loss’, there were no statistically significant differences in change in emotional intensity on Haloperidol. The majority of participants reported some degree of
change in emotional intensity on Haloperidol, compared to only five who experienced no change. Qualitatively, of the 11 participants who reported a change, only one described an increase in sadness when re-experiencing their loss. This participant felt “A bit more sad, more regret, a little bit of guilt”. The other 10 participants described varying degrees of emotional numbness as illustrated in these examples: “I still feel the pain, but maybe more dulled”, “It doesn’t feel as though it has the same unmanageable sadness attached to it”, “A bit less emotionally charged”, “I feel emotionally numb or buffered”, “I feel detached from the emotion”, “No feelings of loss or sadness”, “I’m not traumatised by the thought of it”, “I remember how I feel but I can’t quite feel it” and “It’s not that I’m more sad, but I want reassurances that things are okay”.

On all the psychological probes data together, that is, ‘directed probes’, ‘memories of loss’ and ‘free association’, three prominent affects were identified by coders A for Haloperidol:

- Low drive: Coders A identified eight participants who reported lowered energy, motivation, interest and feeling withdrawn, described in statements like “I think it’s more a decrease in energy, decrease in interest, in wanting to do things”, “Hmm, maybe the drive is missing a little bit”, “I feel not very interested in anything”, “I’m not feeling motivated to do anything challenging”, “So it’s kind of like I think…yes, that’s a very good idea, can we do it tomorrow”, “I feel very, very tired. Less interested and less excited. I feel low-spirited” and “There is a pure dampening of my motivation”. Others reported that it was a huge effort to think about their losses and that they simply did not care to do so. Some felt quite withdrawn, expressed in statements such as “I think it’s a bit of a withdrawal from the world”, “I just feel like withdrawing and closing my eyes” and “I feel an inner sense of
withdrawing into myself”. After leaving the interview sessions, some participants continued to experience the typical effects of Haloperidol, reporting that “I was really low on energy” and “Emotionally, I was just really tired.” Coders B identified this affect in six of the eight participants coders A had originally identified. There was thus 75% agreement between coders A and B.

- **Relaxed:** Not all participants interpreted reduced drive in a negative manner, but rather as a kind of relaxation, which encompassed feeling calm, comfortable, secure, at ease, subdued, content and tired or sleepy. Coders A identified eight participants who described this relaxed feeling in statements like “Actually, in the moment, I feel quite relaxed, quite nice even”, “I feel at ease. Interestingly, in this session, comfortable”, “I feel very relaxed…not a lot of anxiety at all”, “I feel less concerned about the situation, so maybe a slight positive improvement in mood”, “A little more comfortable, more secure, more attached”, “I feel quite content in the way you just described”, “I have felt very calm today” and “I’m still very tired but I feel more in a relaxed way tired”. Coders B however only identified this affect in three of the eight participants originally identified by coders A. There was thus only a 37.5% agreement between coders A and B.

- **Detached:** Coders A identified eight participants who felt detached from their emotions, their memories or from other people. These feelings were evident in statements like “I don’t feel attached to my loved ones, but I know I can rely on them”, “I feel detached from the emotion. Too much effort to think about it”, “My feeling of caring is diminished. I feel buffered”, “I feel indifferent. There’s a lack of feeling of loss really”, “I feel separated from my feelings.”
The thought is completely separated from any emotion” and “I wouldn’t say there is no affect, but there is a diminished feeling”. Coders B identified this affect in the same eight participants originally identified by coders A. There was thus complete agreement between coders A and B.

Based on the psychological probes data, Haloperidol did produce some effects in keeping with predictions. Eight participants felt detached and six reported a reduction in drive (coders A and B were in strong agreement). Eight participants reported a decrease in SEEKING on the ‘directed probes’ and 10 participants described feeling emotionally numb when recalling their ‘memories of loss’. Moreover, there was corroborating evidence from the psychometric data, confirming a decrease in SEEKING on the ANPS. Lastly, there was a trend towards significance indicating some degree of association between the psychometric and qualitative measures of reduced SEEKING.

**Testing hypothesis 3.** Morphine will significantly decrease PANIC/GRIEF, increase PA and significantly improve depressive mood, from baseline, on the quantitative measures. Morphine will reduce PANIC/GRIEF and improve affective valence and mood as qualitatively described in the ‘directed probes’, ‘memories of loss’ and ‘free association’, paradigms.

A series of Wilcoxon tests were conducted to determine whether, compared to baseline, Morphine would significantly reduce PANIC/GRIEF, increase PA and significantly improve mood (see Table 7). The comparison for PANIC/GRIEF was significant, $z = -2.46$, $p = .007$, and in the direction predicted. Morphine reduced PANIC/GRIEF in N=13. According to Cohen’s guidelines, the effect size of this comparison is medium. The comparison for PA was significant, $z = -2.95$, $p = .002$, but in the opposite direction to that predicated. Instead of
increasing PA, Morphine reduced PA in N=13. Although Morphine did not have a significant effect on mood, \( z = -0.23, p = .410 \), MDI scores were lower than baseline in N=10.

A series of Spearman’s Rank-Order correlation analyses were run to assess whether there was any association between the changes in PANIC/GRIEF as measured by the psychometric ANPS and the changes in PANIC/GRIEF as measured by the qualitative ‘directed probes’. The analyses detected no significant associations for Morphine (\( r_s = -.19, p = .239 \)), indicating that the psychometric and qualitative measures were not consistent with one another. On the ANPS, N=13 reported a decrease in PANIC/GRIEF, whereas on the ‘directed probes’, N=6 reported no change in PANIC/GRIEF (explaining why the correlation indicated no association).

On ‘memories of loss’, change in emotional intensity was significantly greater on Morphine, but only when compared to Placebo, and not to any of the other medications. Only three participants reported no change in emotional intensity on Morphine when re-experiencing their memories. Qualitatively, several participants felt less pain and sadness, described as “I feel less negative emotion”, “When I think about it, I don’t feel any pain around it”, “I’m not feeling tearful, I’m not feeling sadness” and “The sadness feels peripheral at this moment”. Others described feeling removed from the emotion connected to it. Examples of such feelings were: “The whole memory feels suspended”, “I feel distant from the emotion, it doesn’t feel distressing”, “I can’t detect any emotions really”, “Hard to connect with the way I was feeling” and “It doesn’t carry any emotional weight thinking about that now”.

A Fischer’s Exact test was used to compare changes in PANIC/GRIEF on Morphine to changes in PANIC/GRIEF on Naltrexone on the ‘directed probes’ specifically. There were no significant associations between changes in PANIC/GRIEF and the opioid-based medication, \( p = .208, V = .26 \). This is understandable given that eight participants qualitatively
reported a decrease in PANIC/GRIEF on Morphine, but only three qualitatively reported an increase in PANIC/GRIEF on Naltrexone.

On all the psychological probes data together, that is, ‘directed probes’, ‘memories of loss’ and ‘free association’, three prominent affects were identified by coders A for Morphine:

- **Relaxed:** Coders A identified eight participants who reported feeling relaxed/content, described variously as calm, comfortable, secure, at ease, subdued, content, tired or sleepy and less anxious. Examples of the kinds of positive sentiments that participants expressed were: “I felt this kind of relaxation, it felt like a calming relaxation, and then it kind of turned into a slight happiness”, “I feel physically relaxed”, “It’s kind of a warm, comfort, almost slightly numb sensation”, “I feel lighter and happier and more hopeful”, “I have a warm fuzzy feeling”, “I feel content and energised”, “I have an overall positive affect. I feel happy” and “I think the anxiety has decreased. I’m actually feeling quite calm”. Some participants continued to feel the effects of Morphine after they had left the interview session. They reported that they continued to feel quite positive, relaxed and content, for example, “I was very relaxed”, “The main thing was a sense of contentment with whatever I was doing” and “I had a “can-do” feeling. It persisted for the rest of the day”. Coders B identified this affect in seven of the eight participants originally identified by coders A. There was thus an 87.5% agreement between coders A and B.

- **Muted pain/detachment:** Coders A identified ten participants who reported a detachment from the negative aspects, pain and/or sadness of their memories, that is, the pain associated with their respective loss was reduced or muted.
Examples of feelings of detachment were “I feel distant from the loss experience”, “I feel indifferent to the loss situation”, “I’m feeling more detached from the negative emotions of that experience”, “I am separated from the feelings around receiving bad news”, “I don’t feel as upset as I normally do”, “I’m not feeling it, and I’m not feeling tearful, I’m not feeling sadness”, “I almost feel less negative emotion than I recall from describing it the first time”, “There’s something more contained about it, it doesn’t feel so horrible”, “I’m remembering the good times”, “What’s coming to mind is enjoyable events with her, not the actual split”, “I feel sadness, but not the severe aching sadness I felt the last time. It feels peripheral at this moment”, “I feel a little annoyed actually, no sadness or pain. Not annoyance at myself, but at him” and “I feel slightly hurt when remembering the loss but the hurt is muted”. Again, some of the effects of Morphine lingered for certain participants. Two participants reported how they continued to feel quite detached, evident in these examples, “An effort was required to engage with what’s out there” and “Towards the evening, I was struck by a feeling of being very very unenthused. Surprising in the circumstances. Interesting live music, but I had no interest or wish to participate. I was noticeably bland”. Coders B identified this affect in seven of the ten participants originally identified by coders A. There was thus a 70% agreement between coders A and B.

• Connected: Coders A identified this affect in eight participants, who either reported feeling an increased desire to be around loved ones or they were more focused on and connected to the positive aspects of their memories. Participants described this increased connectedness as “There is pleasure in relating to others”, “I feel relaxed and comfortable in terms of the people that
are close to me, and interacting with people”, “I do feel relaxed and comfortable in relation to people close to me”, “I feel like I could call someone and they would want to do something with me – they wouldn’t be busy”, “I would like to be around the people I feel safest with”, “I have a desire to be around the people I feel safest with”, “What is right at the forefront is just the experience of the connection, and the leaving part is sort of diminished”, “It doesn’t evoke any negative emotions, aside from the latent warmth about him” and “I feel a fond sense of remembrance”. Coders B identified this affect in five of the eight participants originally identified by coders A. There was thus a 62.5% agreement between coders A and B.

Based on the psychological probes data, it would appear that Morphine did produce some effects in keeping with predictions. Seven participants felt relaxed and seven reported that the pain associated with their loss was muted (relatively strong agreement between coders A and B). Eight participants reported a decrease in PANIC/GRIEF on the ‘directed probes’ and 11 participants described feeling emotionally removed when recalling their ‘memories of loss’. Furthermore, there was corroborating evidence from the psychometric data, confirming the decrease in PANIC/GRIEF on the ANPS.

**Testing hypothesis 4.** Naltrexone will significantly increase PANIC/GRIEF and NA and significantly worsen depressive mood, from baseline, on the quantitative measures. Naltrexone will increase PANIC/GRIEF and worsen affective valence and mood as qualitatively described in the ‘directed probes’, ‘memories of loss’ and ‘free association’, paradigms.

A series of Wilcoxon tests were conducted to determine whether, compared to baseline, Naltrexone would significantly increase PANIC/GRIEF and NA, and significantly
worsen mood (see Table 7). The comparison for PANIC/GRIEF on the ANPS was significant, $z = -1.69$, $p = .046$, but in the opposite direction to that predicted. Naltrexone only increased PANIC/GRIEF in N=5. Naltrexone did not significantly increase NA as predicted, $z = -0.49$, $p = .314$, but only increased NA in N=6. Lastly, Naltrexone did not significantly worsen mood on the MDI, as predicted, $z = -1.29$, $p = .098$, but there was a trend towards this in N=8.

Table 7
Results of Wilcoxon Signed Rank Tests for Opioid Medications

<table>
<thead>
<tr>
<th>Variable</th>
<th>$M$ Positive Ranks</th>
<th>$M$ Negative Ranks</th>
<th>$z$</th>
<th>$p$</th>
<th>$r$</th>
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<td>PANIC/GRIEF</td>
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<td>.007</td>
<td>-0.43</td>
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<td>Opioid Antagonist</td>
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<tr>
<td>PANIC/GRIEF</td>
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<td>9.14</td>
<td>-1.69</td>
<td>.046</td>
<td>-0.30</td>
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<td>NA</td>
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<td>.314</td>
<td>-0.09</td>
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<tr>
<td>MDI</td>
<td>9.13</td>
<td>5.33</td>
<td>-1.29</td>
<td>.098</td>
<td>-0.23</td>
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Note. Opioid Agonist = Morphine. Opioid Antagonist = Naltrexone.

A series of Spearman’s Rank-Order correlation analyses were run to assess whether there was any association between the changes in PANIC/GRIEF as measured by the psychometric ANPS and the changes in PANIC/GRIEF as measured by the qualitative ‘directed probes’. The analyses detected no significant associations for Naltrexone ($r_s = .07$, $p = .405$), indicating that the psychometric and qualitative measures were not consistent with one another. On the ANPS, N=11 reported a decrease in PANIC/GRIEF, whereas on the ‘directed probes’, N=9 reported no change in PANIC/GRIEF (explaining why the correlation analysis indicated no association).

On ‘memories of loss’, change in emotional intensity was significantly greater on Naltrexone, but only when compared to Placebo, and not to any of the other medications.
The majority of participants once again reported some degree of change in emotional intensity on Naltrexone compared to only five who experienced no change. Qualitatively, two participants felt an increase in sadness when re-experiencing their loss and described it as “Again those feelings, me causing all the heartache, they’re stronger” and “I feel more sadness”. Generally, however, participants mostly described having difficulty connecting with the memory and there was very little reference to any specific emotion relating to the memory. They described how “It’s hard to actually feel anything”, “I can’t grasp the feeling”, “It doesn’t feel like I’m emotionally really attached to those memories”, “I just don’t feel like I’m easily getting involved in thinking about these different things” and “The thought is there but not attached to any emotions”.

More so than the other medications, Naltrexone produced a range of relatively extreme affects; two participants were severely depressed – in fact, the interviewer had made a particular reference to this – while three participants had very pleasurable responses to Naltrexone, which is highly unusual. Here are some examples of positive reactions: “What is diminished is my desire, but not my sense of pleasure. I feel a pleasurable not caring about things. Eat drink and be merry”, “I’m definitely feeling a relaxed feeling, physically and emotionally” and “I would definitely say there’s a sense of contentedness. I’m feeling secure, secure within my body.” Two of these participants continued to feel these positive effects for several hours after the session, reporting that “I sat at the cricket in the sun thinking this is Nirvana” and “I felt ‘flippen’ (a colloquial term for the word very) fantastic the whole day”. As mentioned above, two participants were notably feeling depressed, which is evident in their statements “Something is going to go wrong”; “The feelings are stronger. I feel more hopeless about it and that sort of thing” and “I’m despondent, but that despondency has increased. Greater sadness. There’s a greater feeling of that kind, more than baseline and
more than last time. I feel the world wants something from me that I’m not willing to give. Anxiety, yes.”

On all the psychological probes data together, that is, ‘directed probes’, ‘memories of loss’ and ‘free association’, two prominent affects were identified by coders A for Naltrexone.

- Detached: With regards to the feelings of detachment, there was a general absence of affect; some participants only remembered factual information, while others felt like an outside observer. Some said that their memories felt abstract and that they were struggling to bring the memory to mind entirely. Coders A identified nine participants who reported feeling detached either from other people or their memories. These feelings of detachment are clearly illustrated in statement such as “This time, it’s detached and distant”, “I feel minimally removed, but not uncomfortably. It’s there as a factual memory but not as an emotional one,” “I can’t get a clear memory. It’s like all the edges have been blurred around it”, “I need to access the memory to access the feeling but I can’t access the memory”, “It’s almost like there is a distance, almost like I’m an outsider, an observer”, “The thought is there, but not attached to any emotions”, “Ok, so I’ve got the memory back but the feeling is not there”, “Mostly I feel third person-ish about it”, “The memory has no affective tone. It feels blunted”, “So I feel safe, but I do not feel like cared about or bonded to. Not at all mindful of the people in my life”, “Not that phased about other people” and “Maybe I’m less willing to be here. I don’t want to engage.” Coders B identified this affect in seven of the nine participants originally identified by coders A. There was thus a 78% agreement between coders A and B.
Low drive: Coders A identified eight participants who experienced a decrease in drive which mainly encompassed lowered motivation, interest and energy. Some illustrative examples of this are “It’s like a more solemn feeling in general”, “I’m slowly starting to feel less energetic”, “I can’t crank up the energy when I don’t really have it”, “I feel subdued. A general loss of interest”, “Definitely a lack of interest”, “I feel a bit more subdued”, “I don’t really experience the need to go out into the world right now”, “I do feel a decreased need to go out and find anything”, “A state of nothingness really” and “It’s a chore to have thoughts”. Coders B identified this affect in four of the eight participants originally identified by coders A. There was thus only a 50% agreement between coders A and B.

The psychological probes showed that Naltrexone did not increase PANIC/GRIEF or NA, reflected in the lack of references by participants to increases in mental pain caused by separation or loss. This was also corroborated by the psychometric data. Instead, what was most notable was the strong feelings of detachment described by participants, with little reference to any negative emotion. The trend for Naltrexone to worsen mood was in keeping with the study’s predictions.

A series of Wilcoxon tests were conducted to determine whether, compared to Naltrexone, Morphine would significantly decrease avoidance and anxiety and increase security on the SAAM (see Table 8). As predicted, avoidance on Morphine was significantly less than avoidance on Naltrexone in N=11, $z = -1.88, p = .031$. According to Cohen’s guidelines, the effect size of this comparison is medium. There was no significant difference on anxiety between the opioid-based medications, $z = -0.63, p = .265$; anxiety scores were only lower on Morphine compared to Naltrexone in N=6. Similarly, there was no significant
difference on security between the opioid-based medications, $z = -0.88, p = .189$, even though security scores on Morphine were greater compared to Naltrexone in $N=10$.

Table 8

Results of Wilcoxon Signed Rank Tests on the SAAM Measures for Opioid Medications

<table>
<thead>
<tr>
<th>SAAM Variables</th>
<th>$M$ Positive Ranks</th>
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<th>$p$</th>
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<td>8.50</td>
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<td>.189</td>
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</table>

Lastly, Placebo significantly reduced SEEKING for $N=13$, $z = -3.16, p = .002$, (two-tailed as no effect was predicted). There was also a trend for PA to be reduced by Placebo for $N=11$, $z = -1.89, p = .059$. On ‘memories of loss’, change in emotional intensity was significantly associated with each of the medications when compared to Placebo, except for Haloperidol. Six participants reported no change in emotional intensity on Placebo when re-experiencing their memories. Of the ten who did experience a change, seven described the change in emotional intensity as mild. These descriptions were quite varied, and some participants had a relatively positive re-experiencing of their loss, reporting that “It feels a bit easier to speak about than usual”, “I’m feeling a bit more positive” and “I’m feeling more positive”. Others found that their re-experiencing of loss was quite negative, describing that “That’s a much stronger feeling. I have the panic you describe”, “I feel more judgement of myself” and “Separation anxiety is heightened”. On all the psychological probes data together, that is, ‘directed probes’, ‘memories of loss’ and ‘free association’, coders A and B identified a wide range of affects on Placebo, but none were prominent. Some participants experienced positive feelings such as feeling happy, enthusiastic and more interestingly, a sense of acceptance (especially in terms of their memories). Five of the participants reported feeling a kind of coming to terms with or acceptance of their loss – almost nostalgic - described in statements such as “The mind frame I’m in is allowing me to pack the memory
away”, “I feel less sad, I feel like smiling about him today. A fond remembrance”, “I am maybe feeling a bit more resolved, perhaps”, “I feel a bit better about it. I really got over it and left it behind” and “I suppose, if anything, I’m feeling better about it now than I usually would”. Others experienced negative feelings like anxiety, evident in statements like “I’m a bit jittery” and “I do feel a slightly elevated anxiety”; panic, described as “The sadness is a little less and the shock, the panic of it, is a bit more”, “I feel a sense of vulnerability, a fear of loss again” and “The separation-anxiety is heightened” and one participant experienced a reduction in drive, stating that “I feel quite down, subdued, not interested”. Also, as previously mentioned, six participants correctly identified that they were on Placebo.

Summary of results for the whole sample. Dopamine medications (Hypothesis 1 & 2): Contrary to my hypotheses, Madopar decreased SEEKING and PA and had no effect on mood. In line with predictions, Haloperidol decreased SEEKING, although it had no effect on NA and mood. There was a trend towards significance between changes in SEEKING and both DA medications on ‘directed probes’. There were no significant associations between changes in SEEKING as measured by the psychometric ANPS and changes in SEEKING as measured by the qualitative ‘directed probes’ for Madopar but a trend towards significance for Haloperidol. On ‘memories of loss’, there were no statistically significant differences in change in emotional intensity when participants were taking Haloperidol, but there were significant differences on Madopar, but only when compared to Placebo. Prominent affects on Madopar were ‘positively stimulated’ (100% agreement between coders A and B) and ‘negatively stimulated’ (75% agreement between coders A and B). Prominent affects for Haloperidol were ‘low drive’ (75% agreement between coders A and B), ‘detached’ (100% agreement between coders A and B) and ‘relaxed’ (37.5% agreement between coders A and B).

Opioid medications (Hypothesis 3 & 4): In line with predictions, Morphine decreased PANIC/GRIEF, although contrary to hypotheses it decreased PA and had no effect on mood.
Again, contrary to hypotheses, Naltrexone decreased PANIC/GRIEF, had no effect on NA and there was a trend towards worsening of mood. There were no significant associations between changes in PANIC/GRIEF and the opioid-based medication on ‘directed probes’. There were no significant associations between changes in PANIC/GRIEF as measured by the psychometric ANPS and changes in PANIC/GRIEF as measured by the qualitative ‘directed probes’ for Morphine or Naltrexone. On the ‘memories of loss’, there were significant differences in change in emotional intensity when participants were taking the Opioid medications, but only when compared to Placebo. Prominent affects on Morphine were ‘relaxed’ (87.5% agreement between coders A and B), ‘muted pain/detachment’ (70% agreement between coders A and B) and ‘connected’ (62.5% agreement between coders A and B). Prominent affects for Naltrexone were ‘detached’ (78% agreement between coders A and B) and ‘low drive’ (50% agreement between coders A and B). Morphine significantly reduced Avoidance on the SAAM compared to Naltrexone. No significant differences were found for Anxiety and Security between the Opioid-based medications.

**Placebo:** Placebo significantly reduced SEEKING and there was a trend for PA to be reduced. On ‘memories of loss’, change in emotional intensity was significantly associated with each of the medications when compared to the Placebo trial, except for Haloperidol. There were no prominent affects identified by coders A and B.

**Results of Psychometric and Psychological Probes Data Analyses for the Split MDI Sample**

**Subjective psychobehavioural effects of medications.** There were no substantial differences between the two groups with respect to the number of positive and negative psychobehavioural effects reported on Madopar, Naltrexone and Placebo. There were however differences between the groups for Haloperidol and Morphine. On Haloperidol, the Low-MDI group reported more than double the number of negative effects compared to the High-MDI
group. It would appear that the Low-MDI group was more responsive to the DA antagonist than the High-MDI group. On Morphine, the High-MDI group experienced double the number of positive effects compared to the Low-MDI group. It would appear that the High-MDI group was more responsive to the opioid agonist compared to the Low-MDI.

**Baseline descriptives prior to medication.** All results reported under this section refer to a split sample, which was based on the MDI scores. Table 9 presents the means and standard deviations of all four psychometric measures at baseline. The High-MDI group had significantly higher baseline MDI scores compared to the Low-MDI group, $U = 0.50, p <.001$. The two groups did not differ significantly on any of the other baseline measure (all $p$s >.140).

Table 9

<table>
<thead>
<tr>
<th>Measure</th>
<th>Low-MDI $n = 8$</th>
<th>High-MDI $n = 8$</th>
<th>Median Low-MDI</th>
<th>Median High-MDI</th>
<th>U</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEEKING</td>
<td>31.38 (3.58)</td>
<td>29.88 (4.36)</td>
<td>32.00</td>
<td>28.00</td>
<td>21.50</td>
<td>.14</td>
</tr>
<tr>
<td>PANIC/GRIEF</td>
<td>21.38 (6.35)</td>
<td>21.38 (2.56)</td>
<td>23.00</td>
<td>22.00</td>
<td>26.50</td>
<td>.30</td>
</tr>
<tr>
<td>PA</td>
<td>35.50 (3.93)</td>
<td>32.88 (5.46)</td>
<td>35.5</td>
<td>32.00</td>
<td>21.50</td>
<td>.14</td>
</tr>
<tr>
<td>NA</td>
<td>13.13 (1.64)</td>
<td>13.25 (3.62)</td>
<td>13.50</td>
<td>12.50</td>
<td>27.00</td>
<td>.32</td>
</tr>
<tr>
<td>MDI</td>
<td>5.50 (1.92)</td>
<td>11.00 (2.27)</td>
<td>5.50</td>
<td>10.50</td>
<td>0.50</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>ECR_Avoidance</td>
<td>5.42 (0.97)</td>
<td>5.76 (0.95)</td>
<td>5.64</td>
<td>6.00</td>
<td>25.50</td>
<td>.26</td>
</tr>
<tr>
<td>ECR_Anxiety</td>
<td>5.33 (0.72)</td>
<td>5.47 (0.92)</td>
<td>5.47</td>
<td>5.53</td>
<td>27.00</td>
<td>.30</td>
</tr>
</tbody>
</table>

*Note. Means are presented with standard deviations in parentheses. All statistical tests reported were 1 tailed.*

At baseline, no participant in either the Low- or High-MDI group met the criteria for clinical depression according to the cut-offs score of 26 for a diagnosis of major depression on the MDI (see Table 10). After taking Haloperidol, two participants in the Low-MDI group scored more than 26 on the MDI. The opposite effect occurred in the High-MDI group; it was Madopar that caused two participants to score more than 26 on the MDI.
### Table 10
**Descriptive Statistics for MDI in the Low and High MDI-Groups for all Medication Conditions**

<table>
<thead>
<tr>
<th>Medication Condition</th>
<th>Low MDI</th>
<th></th>
<th></th>
<th>High MDI</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count &gt; 26</td>
<td>Percentage</td>
<td>Range</td>
<td>Count &gt; 26</td>
<td>Percentage</td>
<td>Range</td>
</tr>
<tr>
<td>Baseline</td>
<td>0</td>
<td>0</td>
<td>2 – 8</td>
<td>0</td>
<td>0</td>
<td>8 – 15</td>
</tr>
<tr>
<td>Morphine</td>
<td>0</td>
<td>0</td>
<td>0 – 21</td>
<td>1</td>
<td>12.5</td>
<td>4 – 29</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>1</td>
<td>12.5</td>
<td>0 – 31</td>
<td>1</td>
<td>12.5</td>
<td>8 – 26</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2</td>
<td>25</td>
<td>5 – 33</td>
<td>0</td>
<td>0</td>
<td>0 – 14</td>
</tr>
<tr>
<td>Madopar</td>
<td>1</td>
<td>12.5</td>
<td>0 – 30</td>
<td>2</td>
<td>25</td>
<td>5 – 32</td>
</tr>
<tr>
<td>Placebo</td>
<td>0</td>
<td>0</td>
<td>0 – 20</td>
<td>1</td>
<td>12.5</td>
<td>0 – 31</td>
</tr>
</tbody>
</table>

**Descriptives of the psychometric measures across medications.** The means and standard deviations of the psychometric measures across medication conditions for the split MDI sample are shown in Table 11.
Table 11

Descriptives for Psychometric Measures Across Medication Conditions for the Split MDI-Groups

<table>
<thead>
<tr>
<th>Conditions</th>
<th>SEEKING</th>
<th>PANIC/GRIEF</th>
<th>PA</th>
<th>NA</th>
<th>MDI</th>
<th>S_Anx</th>
<th>S_Av</th>
<th>S_Sec</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-MDI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>31.38 (3.58)</td>
<td>21.38 (6.35)</td>
<td>35.50 (3.93)</td>
<td>13.13 (1.64)</td>
<td>5.50 (1.93)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Morphine</td>
<td>21.13 (3.18)</td>
<td>18.13 (2.36)</td>
<td>22.88 (6.99)</td>
<td>11.63 (2.56)</td>
<td>8.13 (7.22)</td>
<td>3.55 (1.21)</td>
<td>2.11 (0.99)</td>
<td>6.05 (0.65)</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>23.25 (5.23)</td>
<td>19.25 (1.28)</td>
<td>24.63 (8.53)</td>
<td>11.75 (3.28)</td>
<td>7.50 (9.87)</td>
<td>3.81 (0.76)</td>
<td>2.43 (0.93)</td>
<td>6.00 (0.51)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>18.50 (8.78)</td>
<td>21.25 (2.31)</td>
<td>21.25 (9.08)</td>
<td>13.88 (4.32)</td>
<td>17.13 (10.37)</td>
<td>3.98 (1.07)</td>
<td>2.73 (1.54)</td>
<td>5.93 (0.82)</td>
</tr>
<tr>
<td>Madopar</td>
<td>22.88 (7.12)</td>
<td>19.25 (4.06)</td>
<td>31.25 (11.09)</td>
<td>14.50 (3.66)</td>
<td>8.50 (1.00)</td>
<td>3.58 (1.36)</td>
<td>2.50 (1.45)</td>
<td>5.80 (0.93)</td>
</tr>
<tr>
<td>Placebo</td>
<td>24.86 (5.54)</td>
<td>18.13 (2.03)</td>
<td>31.38 (8.33)</td>
<td>11.88 (2.47)</td>
<td>6.38 (6.89)</td>
<td>3.68 (0.79)</td>
<td>1.96 (1.04)</td>
<td>6.09 (0.57)</td>
</tr>
<tr>
<td><strong>M (SD)</strong></td>
<td>23.00 (6.97)</td>
<td>17.60 (3.57)</td>
<td>25.67 (9.43)</td>
<td>11.24 (3.16)</td>
<td>11.71 (8.71)</td>
<td>4.16 (1.02)</td>
<td>2.62 (1.19)</td>
<td>9.00 (0.68)</td>
</tr>
<tr>
<td><strong>High-MDI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>29.88 (4.36)</td>
<td>21.37 (2.56)</td>
<td>32.88 (5.46)</td>
<td>13.25 (3.62)</td>
<td>11.00 (2.27)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Morphine</td>
<td>22.13 (7.22)</td>
<td>16.75 (3.11)</td>
<td>24.75 (9.13)</td>
<td>12.13 (2.64)</td>
<td>10.25 (9.44)</td>
<td>3.32 (0.66)</td>
<td>2.95 (1.45)</td>
<td>5.05 (1.03)</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>17.13 (6.08)</td>
<td>19.75 (2.92)</td>
<td>18.75 (7.70)</td>
<td>13.75 (2.76)</td>
<td>16.63 (6.84)</td>
<td>3.39 (0.98)</td>
<td>3.88 (1.16)</td>
<td>4.61 (1.04)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>26.88 (4.45)</td>
<td>16.38 (2.45)</td>
<td>30.50 (5.48)</td>
<td>10.63 (0.74)</td>
<td>5.88 (5.03)</td>
<td>3.50 (1.02)</td>
<td>1.73 (0.43)</td>
<td>5.82 (0.71)</td>
</tr>
<tr>
<td>Madopar</td>
<td>21.00 (8.82)</td>
<td>20.50 (6.78)</td>
<td>25.00 (10.52)</td>
<td>17.13 (7.10)</td>
<td>15.63 (11.38)</td>
<td>3.50 (0.87)</td>
<td>3.12 (1.76)</td>
<td>5.02 (1.23)</td>
</tr>
<tr>
<td>Placebo</td>
<td>21.75 (6.41)</td>
<td>18.25 (5.09)</td>
<td>30.13 (9.30)</td>
<td>13.13 (3.18)</td>
<td>8.25 (9.99)</td>
<td>3.71 (0.72)</td>
<td>2.39 (1.04)</td>
<td>5.71 (0.52)</td>
</tr>
<tr>
<td><strong>M (SD)</strong></td>
<td>23.13 (7.44)</td>
<td>18.83 (6.78)</td>
<td>27.00 (9.69)</td>
<td>13.33 (5.74)</td>
<td>11.27 (10.82)</td>
<td>3.49 (1.22)</td>
<td>2.81 (1.37)</td>
<td>5.24 (4.04)</td>
</tr>
</tbody>
</table>

Note: SEEKING = ANPS seeking sub-scale; PANIC/GRIEF = ANPS panic/grief subscale; POS = PANAS positive sub-scale; NEG= PANAS negative sub-scale; S_Anx = SAAM anxiety sub-scale; S_Av = SAAM avoidance sub-scale; S_Sec = SAAM security sub-scale; MDI = total severity of depression score.
Splitting the sample revealed that the two MDI groups had different responses to the medications. In the Low-MDI group, SEEKING and PA were reduced mostly by the DA antagonist whereas in the High-MDI group, the biggest reductions in SEEKING and PA were caused by the opioid antagonist. Similarly, the DA antagonist caused the biggest increase in MDI scores in the Low-MDI group but the largest decrease in MDI scores in the High-MDI group. Once again, in the High-MDI group, the opioid antagonist caused the largest increase in MDI scores. Thus, in 3 of the 5 psychometric measures (SEEKING, PA and MDI), the Low-MDI group appeared to be more responsive to the DA antagonist, whereas the High-MDI group was more responsive to the opioid antagonist. Lastly, the low-MDI group’s more pronounced response to the DA-based medications was once again reflected in their NA scores; both Haloperidol and Madopar accounted for the largest increases in NA for this group. In the High-MDI group, although the opioid antagonist did result in a slight increase in NA, the largest increase was caused by the DA agonist.

**Testing hypothesis 5.** The magnitude of change for SEEKING, PANAS and MDI on the dopamine-based medications will be significantly different between the low and high baseline-MDI groups (i.e. high and low baseline ‘despair’). The groups will likewise differ in relation to their ‘directed probes’, ‘memories of loss’ and ‘free associations’ on the Dopamine-based medications.

A series of Mann-Whitney $U$ tests were conducted to determine whether the magnitude of change for SEEKING, PANAS and MDI on the DA-based medications was significantly different between the Low and High-MDI groups (see Table 12). There were no significant differences in the magnitude of change between the Low and High-MDI groups for SEEKING, affect or mood on the DA agonist. There were however some significant differences between the groups on the DA antagonist. The change from baseline in SEEKING on Haloperidol was significantly different between the two groups, $U = 11.00, p = \ldots$
.027, (according to Cohen’s guidelines, the effect size of this comparison was large), with the Low-MDI group experiencing a significantly larger reduction in SEEKING. The change in MDI from baseline on Haloperidol was significantly different between the two groups, $U = 6.00, p = .006$, (large effect size), with the Low-MDI group experiencing an increase in depressive mood but the High-MDI group experiencing a reduction in depressive mood. The absolute change was larger in the Low-MDI group. The change in PA from baseline on Haloperidol was significantly different between the two groups, $U = 13.00, p = .046$, (large effect size), with the Low-MDI group experiencing a significantly larger reduction in PA.

The change for NA was not significant.

Table 12
Results of Mann-Whitney U Tests for Dopamine Medications

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low-MDI M Rank</th>
<th>High-MDI M Rank</th>
<th>$Z$</th>
<th>$U$</th>
<th>$p$</th>
<th>$r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine Agonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEEKING</td>
<td>8.25</td>
<td>8.75</td>
<td>-0.21</td>
<td>30.00</td>
<td>.833</td>
<td>0.05</td>
</tr>
<tr>
<td>MDI</td>
<td>8.63</td>
<td>8.38</td>
<td>-0.11</td>
<td>31.00</td>
<td>.916</td>
<td>0.03</td>
</tr>
<tr>
<td>PA</td>
<td>7.56</td>
<td>9.44</td>
<td>-0.79</td>
<td>24.50</td>
<td>.430</td>
<td>0.20</td>
</tr>
<tr>
<td>NA</td>
<td>8.75</td>
<td>8.25</td>
<td>-0.21</td>
<td>30.00</td>
<td>.833</td>
<td>0.05</td>
</tr>
<tr>
<td>Dopamine Antagonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEEKING</td>
<td>11.13</td>
<td>5.88</td>
<td>-2.21</td>
<td>11.00</td>
<td>.027</td>
<td>0.55</td>
</tr>
<tr>
<td>MDI</td>
<td>5.25</td>
<td>11.75</td>
<td>-2.74</td>
<td>6.00</td>
<td>.006</td>
<td>0.69</td>
</tr>
<tr>
<td>PA</td>
<td>10.88</td>
<td>6.13</td>
<td>-2.00</td>
<td>13.00</td>
<td>.046</td>
<td>0.50</td>
</tr>
<tr>
<td>NA</td>
<td>7.25</td>
<td>9.75</td>
<td>-1.07</td>
<td>22.00</td>
<td>.285</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Note. Dopamine Agonist = Madopar. Dopamine Antagonist = Haloperidol.

As to the association between the changes in SEEKING as measured by the ANPS and the changes in SEEKING as measured by the ‘directed probes’, there was no significant association for Madopar in the Low-MDI group, $r_s = .29, p = .247$ or the High-MDI group, $r_s = .36, p = .190$. In the Low-MDI group, N=7 reported a decrease in SEEKING on the ANPS but N=5 reported an increase in SEEKING on ‘directed probes’. In the High-MDI group, N=7 reported a decrease in SEEKING on the ANPS, but N=4 reported an increase in SEEKING on ‘directed probes’ (explaining why the correlation analysis indicated no association). But for Haloperidol, there was a significant association between the two
measures of reduced SEEKING in the Low-MDI group, $r_s = .66, p = .039$, and with a strong effect size. This was a reasonable outcome given that N=7 reported a decrease in SEEKING on the ANPS and N=6 reported a decrease in SEEKING on ‘directed probes’. Within the High-MDI group, analyses detected no significant associations for Haloperidol, $r_s = .10, p = .411$. The High-MDI group, N=4 reported a decrease in SEEKING on the ANPS but only N=2 reported a decrease in SEEKING on the ‘directed probes’.

On ‘memories of loss’, there were no striking differences between the groups with regards to the types of personal loss experienced. The number of romantic disappointments, death of a parent, relative or friend, near-death of parent, relative or friend and relocating to another town or country were the same for both groups. Some minor differences were that the High-MDI group experienced more pet-related deaths. The Low-MDI experienced parental divorce whereas the High-MDI group did not and lastly, the Low-MDI experienced double the number of existential losses compared to the High-MDI group. Furthermore, there was a trend towards a statistically significant association between change in emotional intensity and medication, $p = .072, V = .41$, in the Low-MDI group, with a medium effect size. Change in emotional intensity was significantly associated with Madopar when compared to Placebo ($p = .026$), but not with any of the other medications (all $ps > .076$). For the association between Madopar and Placebo, change in emotional intensity was significantly greater when participants were taking Madopar. Of the eight participants in the Low-MDI group, only 2 experienced no change in emotional intensity when re-experiencing their ‘memories of loss’ on Madopar. Two participants experienced a mild change, three a moderate change, and one an extreme change in emotional intensity. Of the six who experienced a change, five described feeling either less emotional pain or more positive when re-experiencing their memories of loss, for example, “I can bring it to mind, it is not as painful to think about it as previous times”, “So it feels like I don’t, I really don’t have a sad feeling about it right now”,

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“I suppose I’m feeling more hopeful about it” and “The difference is noticing that I don’t feel personally wounded by it”. One patient’s recollection of their ‘memories of loss’ was more painful on Madopar and she described it as “I feel a bit more sad about it. It touches me more than it usually does”. Within the High-MDI group, the analysis detected no significant association between change in emotional intensity and Madopar, \( p = .132, V = .39 \). On Haloperidol, three participants in the Low-MDI group reported no change in emotional intensity compared to two in the High-MDI group. Furthermore, there were two notable difference between the groups. Firstly, two participants in the Low-MDI group reported extreme changes, described as “It’s too much effort to think about it. I feel separated from my feelings” and “It’s hard to access it. I can’t trigger the feeling”, compared to no participants reporting extreme changes in the High-MDI group. Secondly, one participant reported mild changes in the Low-MDI group compared to four participants in the High-MDI group. Some examples of mild to moderate changes in the High-MDI group are “It doesn’t seem to hold the seriousness that it did when I normally think about it”, “So it’s almost like looking back on a sad scene rather than being in it”, “It’s a bit more difficult to feel the emotions” and “I feel a bit more detached from the pain of how it was”. What is common in these examples is that participants in this group generally felt more distanced from their memories. This is consistent with the finding mentioned below that in the High-MDI group, a commonly experienced affect throughout all the psychological probes data, was feeling ‘detached’.

There was a significant association between change in SEEKING and the DA medications, \( p = .032, V = .68 \), with a large effect size, in the Low-MDI group for ‘directed probes’ specifically. N=5 reported an increase in SEEKING when on Madopar and N=6 reported a decrease in SEEKING on Haloperidol. These results indicate that the Low-MDI group qualitatively reported increases in SEEKING on Madopar and decreases in SEEKING on Haloperidol, and the direction of change was consistent with the predicted effects of
Madopar and Haloperidol on SEEKING. There was no significant association between change in SEEKING and the DA medications, $p = .674$, $V = .29$, in the High-MDI group.

On all the psychological probes data together, that is, ‘directed probes’, ‘memories of loss’ and ‘free association’, in the Low-MDI group, five of the eight participants felt ‘positively stimulated’ on Madopar while in the High-MDI group, five of the eight participants felt ‘negatively stimulated’. In the Low-MDI group, four of the eight participants experienced a ‘low drive’ on Haloperidol, while in the High-MDI group, only two participants experienced a reduction in drive. Only three participants in the High-MDI group reported feeling ‘relaxed’; no participants in the Low-MDI reported feeling relaxed on Haloperidol. Six of the eight participants in the High-MDI group reported feeling ‘detached’ compared to two in the Low-MDI group.

**Summary of results for the split MDI-sample.** Dopamine medications. Madopar did not account for any differences between the groups on SEEKING, affect or mood. In contrast, Haloperidol resulted in the Low-MDI group experiencing relatively larger reduction in SEEKING and PA, and an increase in depressive mood, compared to the High-MDI group. On the ‘directed probes’, there was a significant association between change in SEEKING and the DA medications in the Low-MDI group only. There was no significant association between the ‘directed probes’ and the ANPS measures of increased SEEKING for Madopar, in both groups. There was a significant association between the measures for decreased SEEKING on Haloperidol in the low-MDI group, but not the High-MDI group. On the ‘memories of loss’, there was a significance in change in emotional intensity on Madopar when compared to Placebo in the Low-MDI group. Lastly, with regards to prominent affects, the Low-MDI group was relatively more ‘positively stimulated’ on Madopar compared to the High-MDI group. In turn, the High-MDI group felt relatively more ‘detached’ on Haloperidol compared to the Low-MDI group.
Results of Psychometric and Psychological Probes Data Analyses for the Split ECR-Avoidance Sample

Subjective psychobehavioural effects of medications. There were no substantial differences between the two groups with respect to the number of positive and negative psychobehavioural effects reported on Morphine, Naltrexone and Placebo. There were however differences between the High and Low-Avoidance groups for Madopar, with the Low-Avoidance group experiencing almost three times the number of positive effects compared to the High-Avoidance group. This is consistent with the Low-Avoidance group having significantly higher baseline SEEKING scores compared to the High-Avoidance group. On Haloperidol, the High-Avoidance group experienced three times the number of negative effects compared to the Low-Avoidance group.

Baseline descriptives prior to medication. All results reported under this section refer to the split sample, which was based on ECR-Avoidance scores. Table 13 presents the means and standard deviations of all four psychometric measures at baseline. The High-Avoidance group had significantly higher baseline ECR-Avoidance scores compared to the Low-Avoidance group, \( U < 0.01, p = .001 \), providing validation for splitting the sample. The Low-Avoidance group had significantly higher baseline SEEKING scores compared to the High-Avoidance group, \( U = 15.50, p = .041 \). The two groups did not differ significantly on any of the other baseline measure (all \( ps >.056 \)).
Table 13

Baseline Measures by Split ECR-Avoidance-Groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>Low Avoidance</th>
<th>High Avoidance</th>
<th>Median Low Avoidance</th>
<th>Median High Avoidance</th>
<th>U</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEEKING</td>
<td>32.25 (4.17)</td>
<td>29.00 (3.12)</td>
<td>32.50</td>
<td>28.00</td>
<td>15.50</td>
<td>.041*</td>
</tr>
<tr>
<td>PANIC/GRIEF</td>
<td>22.63 (2.26)</td>
<td>20.13 (6.17)</td>
<td>23.00</td>
<td>20.00</td>
<td>22.00</td>
<td>.142</td>
</tr>
<tr>
<td>PA</td>
<td>35.50 (4.84)</td>
<td>32.88 (4.67)</td>
<td>36.50</td>
<td>32.00</td>
<td>20.50</td>
<td>.113</td>
</tr>
<tr>
<td>NA</td>
<td>14.25 (3.24)</td>
<td>12.13 (1.64)</td>
<td>14.00</td>
<td>11.50</td>
<td>17.00</td>
<td>.056</td>
</tr>
<tr>
<td>MDI</td>
<td>8.88 (4.19)</td>
<td>7.63 (2.77)</td>
<td>8.50</td>
<td>8.00</td>
<td>28.00</td>
<td>.337</td>
</tr>
<tr>
<td>ECR_Avoidance</td>
<td>4.91 (0.81)</td>
<td>6.27 (0.43)</td>
<td>5.08</td>
<td>6.33</td>
<td>&lt;0.01</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>ECR_Anxiety</td>
<td>4.99 (0.68)</td>
<td>5.80 (0.74)</td>
<td>5.05</td>
<td>5.99</td>
<td>10.50</td>
<td>.012*</td>
</tr>
</tbody>
</table>

Note. Means are presented with standard deviations in parentheses. All statistical tests reported were 1 tailed.
Descriptives of the psychometric measures across medications. The means and standard deviations of the psychometric measures across medications for the split ECR-Avoidance sample are shown in Table 14. PA was reduced for both groups across all medications, compared to baseline. In the Low-Avoidance group, Morphine caused the greatest reduction in PA, followed by Naltrexone, whereas in the High-Avoidance group, Naltrexone caused the greatest decrease in PA, followed by Morphine. Compared to baseline, NA was reduced by all medications except for Madopar in the Low-Avoidance group, with Morphine causing the largest reduction. For the High-Avoidance group, NA was only reduced on Placebo, remained the same on Haloperidol, and increased on Morphine, Naltrexone and Madopar. PANIC/GRIEF was reduced in both groups across all medications, except for the High-Avoidance group who experienced an increased in PANIC/GRIEF on Madopar. In the Low-Avoidance group, Morphine and Madopar caused the largest decrease in PANIC/GRIEF. In the High-Avoidance group, the greatest decrease in PANIC/GRIEF was caused by Placebo, followed closely by Morphine. In the Low-Avoidance group, Haloperidol and Madopar caused an increase in depression scores compared to baseline but the biggest increase was caused by Madopar. All other medications caused a reduction in depression scores, with the biggest reduction caused by Morphine. In the High-Avoidance group, all medications except Placebo caused an increase in depression scores, with the biggest increase caused by Naltrexone, followed by Haloperidol.

As previously mentioned, the SAAM was not administered at baseline, thus no baseline means were available for comparison. However, when comparing the group means for each sub-scale across all medications on this attachment measure, there was no noteworthy difference between the Low and High-Avoidance groups.
Table 14
**Descriptives for Psychometric Measures Across Medications for the Split ECR-Avoidance-Groups**

<table>
<thead>
<tr>
<th></th>
<th>SEEKING</th>
<th>PANIC/GRIEF</th>
<th>PA</th>
<th>NA</th>
<th>MDI</th>
<th>S_Anx</th>
<th>S_Av</th>
<th>S_Sec</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Avoidance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>32.25 (4.17)</td>
<td>22.63 (2.26)</td>
<td>35.50 (4.84)</td>
<td>14.25 (3.24)</td>
<td>8.88 (4.19)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Morphine</td>
<td>22.88 (3.80)</td>
<td>16.88 (1.64)</td>
<td>23.13 (7.49)</td>
<td>11.25 (1.83)</td>
<td>6.50 (6.39)</td>
<td>3.71 (0.93)</td>
<td>2.66 (1.34)</td>
<td>5.36 (0.84)</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>22.63 (4.21)</td>
<td>19.25 (2.82)</td>
<td>25.00 (9.32)</td>
<td>11.88 (2.95)</td>
<td>8.75 (7.32)</td>
<td>4.02 (0.72)</td>
<td>2.98 (1.17)</td>
<td>5.29 (0.97)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>21.88 (8.98)</td>
<td>19.00 (4.07)</td>
<td>25.38 (8.25)</td>
<td>12.38 (2.97)</td>
<td>10.50 (11.60)</td>
<td>4.14 (1.03)</td>
<td>2.48 (1.58)</td>
<td>5.56 (0.43)</td>
</tr>
<tr>
<td>Madopar</td>
<td>22.13 (9.85)</td>
<td>18.63 (5.88)</td>
<td>29.00 (11.64)</td>
<td>16.38 (5.76)</td>
<td>12.75 (11.41)</td>
<td>3.73 (1.40)</td>
<td>2.77 (1.47)</td>
<td>5.18 (1.04)</td>
</tr>
<tr>
<td>Placebo</td>
<td>24.88 (6.56)</td>
<td>18.75 (2.82)</td>
<td>33.13 (8.36)</td>
<td>13.13 (3.04)</td>
<td>8.13 (9.91)</td>
<td>3.84 (0.54)</td>
<td>2.39 (1.41)</td>
<td>5.78 (0.59)</td>
</tr>
<tr>
<td><strong>M (SD)</strong></td>
<td>24.21 (6.93)</td>
<td>18.86 (3.62)</td>
<td>27.75 (9.19)</td>
<td>12.93 (3.58)</td>
<td>8.86 (8.36)</td>
<td>3.54 (1.05)</td>
<td>2.58 (1.30)</td>
<td>5.55 (0.84)</td>
</tr>
<tr>
<td><strong>High Avoidance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>29.00 (3.12)</td>
<td>20.13 (6.17)</td>
<td>32.88 (4.67)</td>
<td>12.13 (1.64)</td>
<td>7.63 (2.77)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Morphine</td>
<td>20.38 (6.70)</td>
<td>18.00 (3.59)</td>
<td>24.50 (8.78)</td>
<td>12.50 (3.07)</td>
<td>11.88 (9.30)</td>
<td>3.16 (0.95)</td>
<td>2.39 (1.28)</td>
<td>5.75 (1.12)</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>17.75 (7.38)</td>
<td>19.75 (1.49)</td>
<td>18.38 (6.32)</td>
<td>13.63 (3.20)</td>
<td>15.38 (10.64)</td>
<td>3.18 (0.84)</td>
<td>3.32 (1.41)</td>
<td>5.32 (1.23)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>23.50 (7.41)</td>
<td>18.63 (2.88)</td>
<td>26.38 (9.64)</td>
<td>12.13 (4.05)</td>
<td>12.50 (8.26)</td>
<td>3.34 (0.95)</td>
<td>1.98 (0.71)</td>
<td>6.20 (0.87)</td>
</tr>
<tr>
<td>Madopar</td>
<td>21.75 (6.50)</td>
<td>21.13 (5.03)</td>
<td>27.25 (10.90)</td>
<td>15.25 (5.82)</td>
<td>11.38 (11.27)</td>
<td>3.35 (0.75)</td>
<td>2.86 (1.80)</td>
<td>5.64 (1.24)</td>
</tr>
<tr>
<td>Placebo</td>
<td>21.75 (5.37)</td>
<td>17.63 (4.63)</td>
<td>28.38 (8.60)</td>
<td>11.88 (2.64)</td>
<td>6.50 (7.05)</td>
<td>3.55 (0.89)</td>
<td>1.97 (0.42)</td>
<td>6.02 (0.55)</td>
</tr>
<tr>
<td><strong>M (SD)</strong></td>
<td>22.07 (6.82)</td>
<td>19.04 (4.11)</td>
<td>26.04 (8.99)</td>
<td>12.86 (3.55)</td>
<td>11.02 (8.75)</td>
<td>3.66 (0.80)</td>
<td>2.58 (1.32)</td>
<td>5.67 (1.02)</td>
</tr>
</tbody>
</table>

Note: SEEKING = ANPS seeking sub-scale; PANIC/GRIEF = ANPS panic/grief subscale; POS = PANAS positive sub-scale; NEG= PANAS negative sub-scale; S_Anx = SAAM anxiety sub-scale; S_Av = SAAM avoidance sub-scale; S_Sec = SAAM security sub-scale; MDI = total severity of depression score.
Testing hypothesis 6. The magnitude of change for PANIC/GRIEF, PANAS and MDI on the opioid-based medications will be significantly different between the low and high baseline ECR ‘anxious’ and ‘avoidant’ attachment groups (i.e., high and low baseline ‘protest’). The groups will likewise differ in relation to their ‘directed probes’, ‘memories of loss’ and ‘free associations’ on opioid-based medications.

For avoidant attachment, a series of Mann-Whitney $U$ tests were conducted to determine whether the magnitude of change for PANIC/GRIEF, PANAS and MDI on the opioid-based medications would be significantly different between the Low and High-Avoidant groups (see Table 15). There were no significant differences in the magnitude of change between the Low and High-Avoidance groups for PANIC/GRIEF, PA or mood on the opioid-based medications. There were however some significant differences between the groups for NA on both opioid-based medications. The change from baseline in NA scores on Morphine was significantly different between the two groups, $U = 12.50, p = .039$ (large effect size), with the Low-Avoidance group experiencing a significantly larger reduction in NA. The Low-Avoidance group experienced a decrease in NA, whereas the High-Avoidance group experienced a slight increase in NA. The change from baseline in NA on Naltrexone was also significantly different between the two groups, $U = 11.50, p = .030$ (large effect size), with the Low-Avoidance group experiencing a significantly larger reduction in NA.
Table 15

*Results of Mann-Whitney U Tests for Opioid Based Medications*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low Avoidance</th>
<th>High Avoidance</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M Rank</td>
<td>M Rank</td>
<td>z</td>
<td>U</td>
<td>p</td>
</tr>
<tr>
<td>Opioid Agonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANIC/GRIEF</td>
<td>9.56</td>
<td>7.44</td>
<td>-0.90</td>
<td>23.50</td>
<td>.370</td>
</tr>
<tr>
<td>MDI</td>
<td>10.19</td>
<td>6.81</td>
<td>-1.42</td>
<td>18.50</td>
<td>.155</td>
</tr>
<tr>
<td>PA</td>
<td>9.31</td>
<td>7.69</td>
<td>-0.68</td>
<td>25.50</td>
<td>.494</td>
</tr>
<tr>
<td>NA</td>
<td>10.94</td>
<td>6.06</td>
<td>-2.07</td>
<td>12.50</td>
<td>.039*</td>
</tr>
<tr>
<td>Opioid Antagonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANIC/GRIEF</td>
<td>9.75</td>
<td>7.25</td>
<td>-1.06</td>
<td>22.00</td>
<td>.291</td>
</tr>
<tr>
<td>MDI</td>
<td>10.38</td>
<td>6.63</td>
<td>-1.58</td>
<td>17.00</td>
<td>.113</td>
</tr>
<tr>
<td>PA</td>
<td>7.06</td>
<td>9.94</td>
<td>-1.22</td>
<td>20.50</td>
<td>.222</td>
</tr>
<tr>
<td>NA</td>
<td>11.06</td>
<td>5.94</td>
<td>-2.17</td>
<td>11.50</td>
<td>.030*</td>
</tr>
</tbody>
</table>

*Note. Opioid Agonist = Morphine. Opioid Antagonist = Naltrexone. All statistical tests reported were 2 tailed.*

On ‘directed probes’, there was no significant association between change in PANIC/GRIEF and the opioid-based medications, \( p = .413, V = .41 \) and \( p = .293, V = .13 \) in both the Low-and- High- ECR-Avoidance groups respectively. On Morphine, \( N=4 \) in the Low-Avoidance group and \( N=4 \) in the High-Avoidance group reported a decrease in PANIC/GRIEF. On Naltrexone, \( N=2 \) in the Low-Avoidance group and \( N=1 \) in the High-Avoidance group reported an increase in PANIC/GRIEF. These results indicate that the same number of participants in both groups qualitatively reported decreases in PANIC/GRIEF on Morphine and very few participants in both groups qualitatively reported increases in PANIC/GRIEF on Naltrexone.

As to the association between the changes in PANIC/GRIEF as measured by the ANPS and the changes in PANIC/GRIEF as measured by the ‘directed probes’, there was no significant association for Naltrexone, \( r_s = -.10, p = .412 \) in the Low-ECR-Avoidance group. When on Naltrexone, most participants reported a decrease in PANIC/GRIEF on the ANPS, whereas more participants (\( N=5 \)) reported no change in PANIC/GRIEF on the ‘directed
probes’. [No correlation could be run for Morphine because all participants reported experiencing a decrease in PANIC/GRIEF on the ANPS]. Within the High-ECR-Avoidance group, analyses detected no significant associations for Morphine ($r_s = -0.31, p = 0.229$) or Naltrexone ($r_s = 0.36, p = 0.192$). On Morphine, N=5 reported a decrease in PANIC/GRIEF on the ANPS, and N=4 reported a decrease in PANIC/GRIEF on the ‘directed probes’, but N=3 also reported ‘no change’. On Naltrexone, N=7 in the Low-Avoidance group and N=4 in the High-Avoidance group reported a decrease in PANIC/GRIEF on the ANPS, but N=5 in the Low-Avoidance group and N=4 in the High-Avoidance group responded with ‘no change’ on the ‘directed probes’ (explaining why the correlation indicated no association).

On ‘memories of loss’, there were no striking differences between the High and Low ECR-Avoidance groups with respect to the types of personal loss experienced. Also, there were no statistically significant associations between change in emotional intensity during ‘memories of loss’ recall and medication for the Low ($p = 0.129, V = 0.39$) and High ($p = 0.665, V = 0.27$) Avoidance groups. One participant in the Low-Avoidance group compared to two in the High-Avoidance group reported no change in emotional intensity on Morphine. There were four moderate and two mild changes in emotional intensity reported in the Low-Avoidance group, compared to three moderate and two mild changes in emotional intensity in the High-Avoidance group. Some examples of mild to moderate change in the Low-Avoidance group were “Less anxiety if I think about it now”, “Not as distressing as I found it the other times” and “The mental imagery is more positive than it would normally be”. In the High-Avoidance group, some examples of mild to moderate change were “There’s no particular feeling” and “It doesn’t have too much impact on me recalling that”. Qualitatively, there was less psychological pain when participants in the Low-Avoidance group re-experienced their loss compared to the High-Avoidance group who were relatively less engaged with the emotions attached to their loss. Lastly, there was one extreme change
reported in each of the Low and High-Avoidance groups, described as “This is very unusual for me, I feel it’s almost something very destructive” and “I can feel a memory of the feeling, but it’s not even that I can feel it. It’s like a memory of a feeling”, respectively. On Naltrexone, two participants in the Low-Avoidance group compared to three in the High-Avoidance group reported no change in emotional intensity. There were two notable differences between the groups on Naltrexone. Firstly, there were four moderate changes in emotional intensity reported in the Low-Avoidance group, compared to two in the High-Avoidance group. Some examples of moderate change in the Low-Avoidance group are “I think what strikes me is the fact that I feel very tranquil when I think about it”, “Sharp and clear in my mind but the feelings are more sad than angry”, “I feel more at peace with it” and “The pain of loss is erased”. Also, two participants reported extreme changes in emotional intensity in the High-Avoidance group, described as “This one has aroused that uncomfortable, panicky feeling” and “I’m truly trying hard to access them, but I can’t break though something. I can’t get there”, compared to zero in the Low-Avoidance group.

On all the psychological probes data together, that is, ‘directed probes’, ‘memories of loss’ and ‘free association’, four participants in the Low and three in the High-Avoidance group reported feeling ‘relaxed’, four participants in the Low and three in the High-Avoidance group reported feeling ‘muted pain/detachment’, and lastly, two participants in each group reported feeling ‘connected’ on Morphine. The Low and High-Avoidance group’s affective responses to Naltrexone were slightly more varied. Four participants in the Low and three in the High-Avoidance group reported feeling ‘detached’, while three participants experienced a reduction in drive in the High-Avoidance group compared to one in the Low-Avoidance group.

Summary of results for the split ECR-Avoidance sample. Opioid Medications:
Morphine and Naltrexone did not account for any significant differences between the groups
for PANIC/GRIEF, PA or mood. The Low-Avoidance group however experienced a significantly larger reduction in NA on Morphine and Naltrexone. There were no significant association between changes in PANIC/GRIEF and the opioid-based medications on ‘directed probes’. There were no significant associations between the ‘directed probes’ and the ANPS measures for Naltrexone or Morphine. There were no statistically significant associations between change in emotional intensity and medication in both groups for ‘memories of loss’. Lastly, there was little difference between the groups in terms of affects on Morphine. On Naltrexone, the groups varied slightly in that more participants in the High-Avoidance group experienced a reduction in drive compared to the Low-Avoidance group.

Results of Psychometric and Psychological Probes Data Analyses for the Split ECR-Anxiety Sample

Baseline descriptives prior to medication. All results reported under this section refer to the split sample, which was based on ECR-Anxiety scores. Table 16 presents the means and standard deviations of all four psychometric measures at baseline. The High-Anxiety group had significantly higher baseline ECR-Anxiety scores compared to the Low-Anxiety group, \( U = 10.00, p = .011 \) and \( U < 0.01, p < .001 \), once again justifying the split. The Low-Anxiety group had significantly higher baseline PANIC/GRIEF scores compared to the High-Anxiety group, \( U = 16.00, p = .043 \). (Although this is a counter-intuitive finding, it must be noted that in this instance, we are possibly seeing the effects of “extreme” values in a small sample. One participant in the Low-Anxiety group had a high PANIC/GRIEF score and one participant in the High-Anxiety group had a very low PANIC/GRIEF score). The two groups did not differ significantly on any of the other baseline measure (all \( ps > .051 \)).
Table 16  
*Baseline Measures by Split ECR-Anxiety-Groups*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Low Anxiety</th>
<th>High Anxiety</th>
<th>Median Low Anxiety</th>
<th>Median High Anxiety</th>
<th>U</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEEKING</td>
<td>32.38 (4.07)</td>
<td>28.88 (3.09)</td>
<td>33.50</td>
<td>28.00</td>
<td>16.50</td>
<td>.051</td>
</tr>
<tr>
<td>PANIC/GRIEF</td>
<td>23.38 (3.20)</td>
<td>19.38 (5.24)</td>
<td>23.00</td>
<td>20.00</td>
<td>16.00</td>
<td>.043*</td>
</tr>
<tr>
<td>PA</td>
<td>35.25 (5.92)</td>
<td>33.13 (3.40)</td>
<td>37.00</td>
<td>33.50</td>
<td>21.00</td>
<td>.123</td>
</tr>
<tr>
<td>NA</td>
<td>13.88 (3.40)</td>
<td>12.50 (1.77)</td>
<td>13.50</td>
<td>12.50</td>
<td>24.50</td>
<td>.213</td>
</tr>
<tr>
<td>MDI</td>
<td>8.75 (4.53)</td>
<td>7.75 (2.25)</td>
<td>8.50</td>
<td>8.00</td>
<td>27.50</td>
<td>.318</td>
</tr>
<tr>
<td>ECR_Avoidance</td>
<td>5.07 (0.95)</td>
<td>6.11 (0.61)</td>
<td>5.33</td>
<td>6.33</td>
<td>10.00</td>
<td>.011*</td>
</tr>
<tr>
<td>ECR_Anxiety</td>
<td>4.79 (0.62)</td>
<td>6.01 (0.36)</td>
<td>4.94</td>
<td>5.99</td>
<td>&lt;0.01</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

Note. Means are presented with standard deviations in parentheses. All statistical tests reported were 1 tailed.
**Subjective psychobehavioural effects of medications.** As for the split avoidance groups, there were likewise no substantial differences between the two anxiety groups with respect to the number of positive and negative psychobehavioural effects reported on Morphine, Naltrexone and Placebo. There were however differences between the High and Low-Anxiety groups for Madopar, with the Low-Anxiety group experiencing almost three times the number of positive effects compared to the High-Anxiety group; this is similar to the experience of the Low-Avoidance group on Madopar. The Low-Anxiety group also experienced double the number of negative effects on Haloperidol, compared to the High-Anxiety group.

**Descriptives of the psychometric measures across medications.** The means and standard deviations of the psychometric measures across medications for the split ECR-Anxiety sample are shown in Table 17. Compared to baseline, PA was reduced for both groups across all medications. In both groups, Naltrexone and Morphine caused the greatest reductions in PA. Compared to baseline, NA was reduced on all medications except for Madopar in the Low-Anxiety group, with Morphine causing the largest reduction. In the High-Anxiety group, NA was reduced on all medications except for Naltrexone and Madopar, which increased NA. The largest increase in NA by far in this group was caused by Madopar. Interestingly, Madopar caused the biggest increase in NA in both Anxiety groups, as it did in both the MDI and Avoidance groups. PANIC/GRIEF was reduced in both groups across all medications, except for the High-Anxiety group who experienced an increase in PANIC/GRIEF on Madopar and Naltrexone. In the Low-Anxiety group, Morphine caused the largest decrease in PANIC/GRIEF. In the High-Anxiety group, Placebo caused the greatest decrease in PANIC/GRIEF followed by Morphine. In the Low-Anxiety group, Naltrexone, Haloperidol and Madopar caused an increase in depression scores compared to baseline with the biggest increase caused by Madopar. Morphine caused a reduction in depression scores in this group.
In the High-Anxiety group, all medications except Placebo caused an increase in depression scores. The biggest increase in depression scores compared to baseline was caused by Naltrexone, followed by Madopar. Lastly, as regards the SAAM, when comparing the group means for each sub-scale across all medications on this attachment measure, there was no noteworthy difference between the Low and High-Anxiety groups.
Table 17
Descriptives for Psychometric Measures Across Medications for the Split ECR-Anxiety-Groups

<table>
<thead>
<tr>
<th></th>
<th>SEEKING</th>
<th>PANIC/GRIEF</th>
<th>PA</th>
<th>NA</th>
<th>MDI</th>
<th>S_Anx</th>
<th>S_Av</th>
<th>S_Sec</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>32.38 (4.07)</td>
<td>23.38 (3.20)</td>
<td>35.25 (5.92)</td>
<td>13.88 (3.40)</td>
<td>8.75 (4.53)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Morphine</td>
<td>21.38 (4.17)</td>
<td>16.63 (1.41)</td>
<td>21.50 (8.02)</td>
<td>11.63 (2.07)</td>
<td>8.25 (8.55)</td>
<td>3.27 (1.16)</td>
<td>2.57 (1.39)</td>
<td>5.69 (1.01)</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>21.13 (5.59)</td>
<td>19.00 (2.93)</td>
<td>21.38 (9.72)</td>
<td>12.88 (3.52)</td>
<td>11.50 (10.92)</td>
<td>3.77 (0.74)</td>
<td>2.86 (1.21)</td>
<td>5.48 (1.09)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>22.13 (8.72)</td>
<td>18.88 (3.91)</td>
<td>23.38 (8.88)</td>
<td>13.13 (4.67)</td>
<td>10.75 (10.95)</td>
<td>4.13 (1.03)</td>
<td>2.04 (1.10)</td>
<td>5.93 (0.57)</td>
</tr>
<tr>
<td>Madopar</td>
<td>22.38 (9.66)</td>
<td>17.88 (5.54)</td>
<td>29.25 (11.88)</td>
<td>15.25 (6.04)</td>
<td>11.75 (11.79)</td>
<td>3.07 (0.73)</td>
<td>2.77 (1.47)</td>
<td>5.34 (1.10)</td>
</tr>
<tr>
<td>Placebo</td>
<td>24.13 (6.79)</td>
<td>18.50 (2.45)</td>
<td>30.63 (9.67)</td>
<td>13.25 (3.54)</td>
<td>8.13 (11.21)</td>
<td>3.68 (0.36)</td>
<td>2.39 (1.43)</td>
<td>5.93 (0.64)</td>
</tr>
<tr>
<td><strong>M (SD)</strong></td>
<td>23.55 (7.22)</td>
<td>18.70 (3.75)</td>
<td>26.13 (9.99)</td>
<td>13.09 (3.82)</td>
<td>10.16 (9.26)</td>
<td>3.53 (0.94)</td>
<td>2.46 (1.33)</td>
<td>5.79 (0.84)</td>
</tr>
<tr>
<td><strong>High Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>28.88 (3.09)</td>
<td>19.38 (5.24)</td>
<td>33.13 (3.40)</td>
<td>12.50 (1.77)</td>
<td>7.75 (2.25)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Morphine</td>
<td>21.88 (6.73)</td>
<td>18.25 (3.58)</td>
<td>26.13 (7.61)</td>
<td>12.13 (3.04)</td>
<td>8.25 (8.55)</td>
<td>3.61 (0.74)</td>
<td>2.48 (1.24)</td>
<td>5.41 (0.99)</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>19.25 (7.25)</td>
<td>20.00 (1.07)</td>
<td>22.00 (7.56)</td>
<td>12.63 (2.88)</td>
<td>12.63 (8.48)</td>
<td>3.43 (1.01)</td>
<td>3.45 (1.32)</td>
<td>5.13 (1.09)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>23.25 (7.76)</td>
<td>18.75 (3.11)</td>
<td>28.38 (8.26)</td>
<td>11.38 (1.30)</td>
<td>12.25 (9.16)</td>
<td>3.36 (0.96)</td>
<td>2.43 (1.36)</td>
<td>5.82 (0.92)</td>
</tr>
<tr>
<td>Madopar</td>
<td>21.50 (6.74)</td>
<td>21.88 (4.85)</td>
<td>27.00 (10.58)</td>
<td>16.38 (5.53)</td>
<td>12.38 (10.91)</td>
<td>4.01 (1.26)</td>
<td>2.86 (1.80)</td>
<td>5.48 (1.23)</td>
</tr>
<tr>
<td>Placebo</td>
<td>22.50 (5.45)</td>
<td>17.88 (4.88)</td>
<td>30.88 (7.95)</td>
<td>11.75 (1.83)</td>
<td>6.50 (4.72)</td>
<td>3.71 (1.01)</td>
<td>1.97 (0.33)</td>
<td>5.87 (0.52)</td>
</tr>
<tr>
<td><strong>M (SD)</strong></td>
<td>22.73 (6.66)</td>
<td>19.20 (3.98)</td>
<td>27.66 (8.11)</td>
<td>12.70 (3.29)</td>
<td>9.71 (7.94)</td>
<td>3.68 (0.93)</td>
<td>2.70 (1.28)</td>
<td>5.43 (0.99)</td>
</tr>
</tbody>
</table>

Note: SEEKING = ANPS seeking sub-scale; PANIC/GRIEF = ANPS panic/grief subscale; POS = PANAS positive sub-scale; NEG= PANAS negative sub-scale; S_Anx = SAAM anxiety sub-scale; S_Av = SAAM avoidance sub-scale; S_Sec = SAAM security sub-scale; MDI = total severity of depression score.
**Testing hypothesis 6.** The magnitude of change for PANIC/GRIEF, PANAS and MDI on the opioid-based medications will be significantly different between the low and high baseline ECR ‘anxious’ and ‘avoidant’ attachment groups (i.e., high and low baseline ‘protest’). The groups will likewise differ in relation to their ‘directed probes’, ‘memories of loss’ and ‘free associations’ on the Opioid-based medications.

For anxious attachment, a series of Mann-Whitney *U* tests were conducted to determine whether the magnitude of change for PANIC/GRIEF, PANAS and MDI on the opioid-based medications would be significantly different between the Low and High-Anxiety attachment groups (see Table 18). There were no significant differences in the magnitude of change between the Low and High-Anxiety groups for PANIC/GRIEF, affect or mood on the opioid-based medications. Although not significant, there was a trend towards significance in the Low-Anxiety group for Morphine, which accounted for the largest decrease in PANIC/GRIEF on ANPS, with a medium effect size.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low Anxiety</th>
<th>High Anxiety</th>
<th>z</th>
<th>U</th>
<th>p</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioid Agonist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANIC/ GRIEF</td>
<td>10.69</td>
<td>6.31</td>
<td>-1.85</td>
<td>14.50</td>
<td>.065</td>
<td>0.46</td>
</tr>
<tr>
<td>MDI</td>
<td>8.81</td>
<td>8.19</td>
<td>-0.26</td>
<td>29.50</td>
<td>.792</td>
<td>0.07</td>
</tr>
<tr>
<td>PA</td>
<td>10.25</td>
<td>6.75</td>
<td>-1.47</td>
<td>18.00</td>
<td>.141</td>
<td>0.37</td>
</tr>
<tr>
<td>NA</td>
<td>9.31</td>
<td>7.69</td>
<td>-0.69</td>
<td>25.50</td>
<td>.491</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Opioid Antagonist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANIC/ GRIEF</td>
<td>10.44</td>
<td>6.56</td>
<td>-1.64</td>
<td>16.50</td>
<td>.102</td>
<td>0.41</td>
</tr>
<tr>
<td>MDI</td>
<td>9.56</td>
<td>7.44</td>
<td>-0.90</td>
<td>23.50</td>
<td>.370</td>
<td>0.23</td>
</tr>
<tr>
<td>PA</td>
<td>9.75</td>
<td>7.25</td>
<td>-1.06</td>
<td>22.00</td>
<td>.228</td>
<td>0.27</td>
</tr>
<tr>
<td>NA</td>
<td>9.19</td>
<td>7.81</td>
<td>-0.58</td>
<td>26.50</td>
<td>.561</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Note.* Opioid Agonist = Morphine. Opioid Antagonist = Naltrexone. All statistical tests reported were 2 tailed.
On ‘directed probes’, there was no significant association between change in PANIC/GRIEF and the opioid-based medications, $p = .431$, $V = .17$ and $p = .075$, $V = .41$ for the Low- and High-ECR-Anxiety groups, but there was a trend towards significance, with a medium effect size, in the High-Anxiety group for Morphine. N=2 reported a decrease in PANIC/GRIEF in the Low-Anxiety group but in the High-Anxiety group, N=6 reported a decrease in PANIC/GRIEF. This result indicates that more participants in the High-Anxiety group qualitatively reported a decrease in PANIC/GRIEF on Morphine, which is a reasonable finding. On Naltrexone, N=2 in the Low-Anxiety group and N=1 in the High-Anxiety group reported an increase in PANIC/GRIEF. This result indicates that very few participants in both groups qualitatively reported an increase in PANIC/GRIEF on Naltrexone.

As to the association between the changes in SEEKING as measured by the ANPS and the changes in SEEKING as measured by the ‘directed probes’, there was no significant association for Naltrexone ($r_s = -.10$, $p = .412$), within the Low-Anxiety group. When on Naltrexone, nearly all participants reported a decrease in PANIC/GRIEF on the ANPS, whereas more participants reported no change in PANIC/GRIEF on ‘directed probes’. [Once again, no correlation could be run for Morphine because all participants reported experiencing a decrease in PANIC/GRIEF on the ANPS]. Within the High-Anxiety group, analyses detected no significant associations for Morphine ($r_s = .15$, $p = .363$) or Naltrexone ($r_s = .36$, $p = .192$). For Morphine and Naltrexone, most participants reported an increase or decrease in PANIC/GRIEF on the ANPS, whereas on the ‘directed probes’, most participants reported no change or a decrease in PANIC/GRIEF (possibly explaining why the correlation indicated no association).

On ‘memories of loss’, there were no striking differences between the High and Low-Anxiety groups with respect to the types of personal loss experienced. There were also no significant associations between change in emotional intensity during ‘memories of loss’
recall and medication for the Low \((p = .329, V = .33)\) and High \((p = .619, V = .27)\) -Anxiety groups. Six participants in each group reported some change in emotional intensity on Morphine and the range of reported emotional changes was quite similar between the groups. In both groups, two participants reported no change in emotional intensity. Four participants reported a moderate change in the High-Anxiety group, described as “There’s no sense of panic that I don’t mean anything to him anymore”, “It feels like I can direct my thoughts quite clearly now and I can look into things” and “I can feel some of the memory of the distress, but it’s distant”, compared to three in the Low Anxiety group. In the Low-Anxiety group, some examples of moderate change are “The general affective tone is not very catastrophic”, “It feels somehow in a way slightly more out of my mental grasp” and “I’m unable to intensely experience that now”. There was also one participant who reported an extreme change in both the Low and High-Anxiety groups, described as “I can’t, I can’t grip it, it’s actually the strangest thing” and “I’m not feeling it. It’s so weird, such a weird thing. Anyway, I’m not feeling it”, respectively. In both groups, there was a lack of negative affect in general and difficulty accessing the loss when participants were re-experiencing their memories. The range of reported emotional changes was also quite similar between the groups on Naltrexone. In both groups, three participants reported no change in emotional intensity and three participants in each group reported a moderate change. In the Low-Anxiety group, some examples of moderate change in emotional intensity are “It doesn’t feel like I’m emotionally attached to those memories”, “The memory has no affective tone” and “Mostly, I feel third-personish about it”. In the High-Anxiety group, some examples of moderate change in emotional intensity are “It makes me feel like crying. The increase stress of anxiousness and sadness”, “I’m just so disconnected, I don’t feel so agitated” and “I don’t feel any pangs. I feel carefree. It doesn’t bother me”. Lastly, there was one participant who reported an extreme change in both the Low and High-Anxiety groups, described as “It’s
such a stark contrast compared to originally telling you about it. It seems a little abstract at the moment” and “I mean I remember it but it’s like watching a movie that has nothing to do with me”, respectively. As with Morphine, the emotional tone of the re-experienced memories generally lacked negative affect and most participants described feeling removed or distanced from their memories.

On all the psychological probes data together, that is, ‘directed probes’, ‘memories of loss’ and ‘free association’, there were three notable differences between the group’s affective responses. On Naltrexone, five participants in the High-Anxiety group felt ‘detached’ compared to two in the Low-Anxiety group. On Morphine, five participants in the Low-Anxiety group felt ‘muted pain/detachment’ compared to two in the High Anxiety group. On Morphine, three participants in the High-Anxiety group reported feeling more ‘connected’ compared to zero in the Low-Anxiety group. The groups did not differ with respect to feeling ‘relaxed’ on Morphine or ‘low drive’ on Naltrexone.

**Summary of results for the split ECR-Anxiety sample. Opioid Medications:**

Morphine and Naltrexone did not account for any significant differences between the groups for PANIC/GRIEF, affect or mood. There was a trend towards significance in the Low-Anxiety group for Morphine, which accounted for the largest decrease in PANIC/GRIEF on the ANPS. There were no significant association between changes in PANIC/GRIEF and the opioid-based medications on ‘directed probes’, but there was a trend towards significance in the High-Anxiety group on Morphine. There were no significant associations between the ‘directed probes’ and the ANPS measures for Naltrexone or Morphine. There were no statistically significant associations between change in emotional intensity during ‘memories of loss’ recall and medication. Lastly, the groups did differ with respect to their prominent affects. More participants in the High-Anxiety group reported feeling ‘detached’ compared to the Low-Anxiety group on Naltrexone; more participants reported feeling ‘muted
pain/detachment’ on Morphine in the Low-Anxiety group compared to the High-Anxiety group and more participants in the High-Anxiety group reported feeling ‘connected’ on Morphine compared to zero in the Low-Anxiety group.

**Overall Summary of Results for Psychometric and Psychological Probes data**

**Whole sample** (see Table 19):

Hypothesis One: *Madopar will increase SEEKING, PA and significantly improve mood, relative to baseline, on the psychometric measures and psychological probes data.*

Madopar significantly reduced SEEKING and PA and had no significant effect on mood. There was a trend towards significance on the ‘directed probes’, indicating that a majority of participants qualitatively reported an increase in SEEKING. There was no significant association between the psychometric (ANPS) and qualitative (‘directed probes’) measures of increased SEEKING, indicating that psychometrically participants reported reduced SEEKING whereas qualitatively, they reported increased SEEKING. Two prominent affects were identified: ‘feeling positively stimulated’ and ‘feeling negatively stimulated’; in other words, a majority of participants felt ‘stimulated’ but they valenced the experience differently. Change in emotional intensity for ‘memories of loss’ was significantly associated with Placebo, but not to any other medication.

Hypothesis Two: *Haloperidol will significantly decrease SEEKING, increase NA and significantly worsen mood, relative to baseline, on the psychometric measures and psychological probes data.* Haloperidol significantly reduced SEEKING but did not significantly worsen mood or NA. There was a trend towards significance on the ‘directed probes’, indicating that a majority of participants qualitatively reported a decrease in SEEKING. There was a trend towards significance between the psychometric (ANPS) and qualitative (‘directed probes’) measures of reduced SEEKING, indicating that a majority of participants reported reduced SEEKING on both measures. Three prominent affects were
identified: ‘low drive’, ‘detached’ and ‘relaxed’. There were no statistically significant differences in change in emotional intensity for ‘memories of loss’.

Hypothesis Three: Morphine will significantly decrease PANIC/GRIEF, increase PA and significantly improve mood, relative to baseline, on the psychometric measures and psychological probes data. Morphine significantly reduced PANIC/GRIEF but did not improve PA or mood. There was no significant association on the ‘directed probes’. There was no significant association between the psychometric (ANPS) and qualitative (‘directed probes’) measures of reduced PANIC/GRIEF, indicating that psychometrically participants reported reduced PANIC/GRIEF whereas qualitatively, eight reported no change in PANIC/GRIEF. Three prominent affects were identified: ‘relaxed’, ‘muted pain/detachment’ and ‘connected’. Change in emotional intensity for ‘memories of loss’ was significantly associated with Placebo, but not to any other medication.

Hypothesis Four: Naltrexone will significantly increase PANIC/GRIEF and NA and significantly worsen mood, relative to baseline, on the psychometric measures and psychological probes data. Naltrexone significantly reduced PANIC/GRIEF and did not significantly increase NA or worsen mood. There was a trend towards Naltrexone worsening mood. There was no significant association on the ‘directed probes’, indicating that most participants did not qualitatively report any change in the increase of PANIC/GRIEF. There was no significant association between the psychometric (ANPS) and qualitative (‘directed probes’) measures of increased PANIC/GRIEF, indicating that psychometrically most participants reported reduced PANIC/GRIEF whereas qualitatively, most of the participants reported no change in PANIC/GRIEF. Two prominent affects were identified: ‘detached’ and ‘low drive’. Change in emotional intensity for ‘memories of loss’ was significantly associated with Placebo, but not to any other medication.

Although no specific predictions were made for Placebo, it significantly reduced
SEEKING, but had no effect on affect or mood. No prominent affects were identified.

**Split MDI sample** (see Table 19):

Hypothesis Five: *The magnitude of change for SEEKING, PANAS and MDI on the dopamine-based medications will be significantly different between the low and high baseline-MDI groups (i.e. high and low baseline ‘despair’) on the psychometric measures and psychological probes data.* Madopar did not account for any significant differences between the Low and High-MDI groups on SEEKING, affect or mood. Haloperidol accounted for significant differences between the Low and High-MDI groups on SEEKING, PA and mood. Haloperidol reduced SEEKING and PA and worsened mood to a greater extent in the Low-MDI group. Haloperidol did not have a differential effect on NA.

There was a significant association on the ‘directed probes’ in the Low-MDI group, indicating that most participants in this group, but not the High-MDI group, qualitatively reported an increase in SEEKING on Madopar and a decrease in SEEKING on Haloperidol, in keeping with expected medication effects. There was no significant association between the psychometric (ANPS) and qualitative (‘directed probes’) measures of increased SEEKING in both groups on Madopar. This result indicated that in both groups, most participants reported a decrease in SEEKING on the ANPS, but several participants qualitatively reported an increase in SEEKING on the ‘directed probes’ on Madopar. But on Haloperidol, there was a significant association between the two measures in the Low-MDI group. Participants in this group, but not the High-MDI group, reported a decrease in SEEKING on the ANPS and on the ‘directed probes’. In the high-MDI group, more participants reported a decrease in SEEKING on the ANPS compared to the ‘directed probes’. The Low-MDI group was relatively more ‘positively stimulated’ on Madopar compared to the High-MDI group who felt ‘negatively stimulated’. The High-MDI group felt relatively more ‘detached’ on Haloperidol compared to the Low-MDI group. There was a
significance in change in emotional intensity for ‘memories of loss’ on Madopar, compared to Placebo, in the Low-MDI group, but not the High-MDI group.

**Split ECR-Avoidance sample** (see Table 19):

Hypothesis Six: *The magnitude of change for PANIC/GRIEF, PANAS and MDI on the opioid-based medications will be significantly different between the low and high baseline-ECR ‘anxious’ and ‘avoidant’ attachment groups (i.e., high and low baseline ‘protest’) on the psychometric measures and psychological probes data.* Morphine and Naltrexone did not account for any significant differences between the Avoidance groups on PANIC/GRIEF, PA or mood. Morphine and Naltrexone significantly reduced NA in the Low-Avoidance group. There was no significant association on the ‘directed probes’ on Morphine or Naltrexone in both groups. This result indicated that the same number of participants in both groups qualitatively reported decreases in PANIC/GRIEF on Morphine and very few participants in both groups qualitatively reported increases in PANIC/GRIEF on Naltrexone. There was no significant association between the psychometric (ANPS) and qualitative (‘directed probes’) measures of PANIC/GRIEF in the High-Avoidance group for Morphine or Naltrexone. This result indicated that participants in this group reported a decrease in PANIC/GRIEF on the ANPS, but often reported ‘no change’ on the ‘directed probes’ on Morphine and Naltrexone. Furthermore, there was no significant association between the psychometric (ANPS) and qualitative (‘directed probes’) measures of PANIC/GRIEF in the Low-Avoidance group for Naltrexone, indicating that most participants in this group reported a decrease in PANIC/GRIEF on the ANPS compared to the ‘directed probes’, where ‘no change’ was mostly reported. No correlation between the two measures could be run for Morphine in the Low-Avoidance group because all participants in this group reported a decrease in PANIC/GRIEF on the ANPS. There was no statistically significant change in emotional intensity for the ‘memories of loss’ in either group on Morphine or
Naltrexone. There were no noteworthy differences between the group’s affective responses to Morphine. On Naltrexone, three participants experienced a reduction in drive in the High-Avoidance group compared to one in the Low-Avoidance group.

**Split ECR-Anxiety sample** (see Table 19):

Morphine and Naltrexone did not account for any significant differences between the groups on PANIC/GRIEF, affect or mood. There was a trend towards significance for Morphine to decrease PANIC/GRIEF on the ANPS in the Low-Anxiety group. There was a trend towards a significant association on the ‘directed probes’ in the High-Anxiety group, indicating that most participants in this group, but not the Low-Anxiety group, qualitatively reported a decrease in PANIC/GRIEF on Morphine. On Naltrexone, there was no significant association in both groups on the ‘directed probes’, since very few participants in either group qualitatively reported an increase in PANIC/GRIEF. There was no significant association between the psychometric (ANPS) and qualitative (‘directed probes’) measures of PANIC/GRIEF in the High-Anxiety group for Morphine or Naltrexone. This result indicated that most participants in this group reported a decrease in PANIC/GRIEF on the ANPS compared to the ‘directed probes’, where mostly no change was reported. Furthermore, there was no significant association between the psychometric (ANPS) and qualitative (‘directed probes’) measures of PANIC/GRIEF in the Low-Anxiety group for Naltrexone, indicating that most participants in this group reported a decrease in PANIC/GRIEF on the ANPS compared to the ‘directed probes’, where no change was mostly reported. No correlation between the two measures could be run for Morphine in the Low-Anxiety group because all participants in this group reported a decrease in PANIC/GRIEF on the ANPS. There was no statistically significant association between change in emotional intensity when recalling ‘memories of loss’ and the opioid-based medications between the groups. More participants
in the High-Anxiety group reported feeling ‘detached’ on Naltrexone and more participants reported feeling ‘muted pain/detachment’ on Morphine in the Low-Anxiety group.

Table 19
Summary of Results

<table>
<thead>
<tr>
<th></th>
<th>Madopar</th>
<th>Haloperidol</th>
<th>Morphine</th>
<th>Naltrexone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEEKING</td>
<td>reduced</td>
<td>reduced</td>
<td>reduced</td>
<td>reduced</td>
<td>reduced</td>
</tr>
<tr>
<td>PANIC/GRIEF</td>
<td>reduced</td>
<td></td>
<td>reduced</td>
<td>reduced</td>
<td>trend towards significance to reduce</td>
</tr>
<tr>
<td>SEEKING</td>
<td>reduced</td>
<td>reduced</td>
<td>reduced</td>
<td>reduced</td>
<td>no effect</td>
</tr>
<tr>
<td>PA</td>
<td>no effect</td>
<td>no effect</td>
<td>no effect</td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
<td>NA</td>
<td>no effect</td>
<td>no effect</td>
<td>no effect</td>
<td>no effect</td>
<td>trend towards significance to reduce</td>
</tr>
<tr>
<td>MDI</td>
<td>no effect</td>
<td>no effect</td>
<td>no effect</td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
<td>Directed Probes</td>
<td>trend towards significance. N=9 reported increased SEEKING</td>
<td>trend towards significance. N=8 reported reduced SEEKING</td>
<td>no effect</td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
<td>ANPS vs Directed Probes</td>
<td>no association</td>
<td>trend towards significant association</td>
<td>no association</td>
<td>no association</td>
<td>no association</td>
</tr>
<tr>
<td>Change in emotional intensity on memories of loss</td>
<td>greater when compared to Placebo. 10 reported feeling more positive.</td>
<td>greater when compared to Placebo. N =11 reported feeling emotionally numbness with respect to memories.</td>
<td>greater when compared to Placebo.</td>
<td>greater when compared to Placebo. N=9 reported difficulty connecting with memories.</td>
<td>N=10 reported feeling either positive or negative changes in emotional intensity of memories.</td>
</tr>
<tr>
<td>Split MDI Sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEEKING</td>
<td>no effect</td>
<td>reduced for Low-MDI group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANIC/GRIEF</td>
<td>no effect</td>
<td>reduced for Low-MDI group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>Madopar: no effect</td>
<td>Haloperidol: no effect</td>
<td>Morphine: increased for Low-MDI group</td>
<td>Naltrexone: no effect</td>
<td>Placebo: no effect</td>
</tr>
<tr>
<td>MDI</td>
<td>Directed Probes: significant for Low-MDI; N=5 reported increased SEEKING</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANPS vs Directed Probes: no association</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in emotional intensity on memories of loss: greater when compared to Placebo for Low-MDI group. N=5 reported feeling less emotional pain or positive</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Prominent Affects: N=5 ‘positively stimulated’ in Low-MDI group; N=5 ‘negatively stimulated’ in High-MDI group</td>
<td>N=4 ‘low-drive’ in Low-Avoidance group; N=6 ‘detached’ in High-MDI group</td>
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</tbody>
</table>

**Split ECR-Avoidance Sample**

SEEKING PANIC/GRIEF
PA
NA

| MDI | Directed Probes: no effect | ANPS vs Directed Probes: no association | Change in emotional intensity: no effect | | |

168
on memories of loss

<table>
<thead>
<tr>
<th></th>
<th>Madopar</th>
<th>Haloperidol</th>
<th>Morphine</th>
<th>Naltrexone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prominent Affects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=4 ‘relaxed’ and N=4 ‘muted pain/detachment’ in Low-Avoidance group; N=3 ‘relaxed’ and N=3 ‘muted pain/detachment’ in High-Avoidance group</td>
<td></td>
<td></td>
<td>N=4 ‘detached’ and N=1 ‘low drive’ in Low-Avoidance group; N=3 ‘detached’ and N=3 ‘low drive’ in High-Avoidance group</td>
<td></td>
</tr>
</tbody>
</table>

**Split ECR-Anxiety Sample**

**SEEKING**

**PANIC/GRIEF**

trend towards significance for Low-Anxiety group

**PA**

no effect

**NA**

no effect

**MDI**

no effect

**Directed Probes**

trend towards significance for High-Anxiety group; N=6 reported decrease in PANIC/GRIEF

**ANPS vs Directed Probes**

no association

**Change in emotional intensity on memories of loss**

Prominent Affects

N=5 ‘muted pain/detachment’ in Low-Anxiety group; N=2 ‘muted pain/detachment’ in High-Anxiety group

N=5 ‘detached’ in High-Anxiety group; N=2 ‘detached’ in Low-Anxiety group

Note. Blank spaces in the table indicate that those particular relationships were not explored.
CHAPTER FIVE:

Discussion

Canonically, the separation-distress response to social loss manifests firstly as PANIC, expressed as ‘protest’, followed by GRIEF, expressed as ‘despair’, if the ‘protest’ behaviour does not lead to the desired reunion. Panksepp’s (1998) claim is that the despair phase of the separation-distress response is the normal prototype of depression, that is, sadness, hopelessness, anergia and anhedonia (Solms & Panksepp, 2010). Within the theoretical framework of affective neuroscience, major depression is thus characterised by an overactivated PANIC/GRIEF system and an underactivated SEEKING system (Panksepp, 2004). Empirical support for this view is well established in the preclinical literature but the evidence in humans is limited, at best. In light of this, the PANIC/GRIEF and SEEKING systems were artificially stimulated in 16 healthy volunteers. Both psychometric questionnaires and psychological probes were used to identify, measure and qualitatively characterise the anticipated effects of these manipulations. The aims of the study were to, firstly, establish whether a stimulated PANIC/GRIEF system and a dampened SEEKING system would lead to depressive affects that are homologous to the mammalian ‘protest’ and ‘despair’ behaviours and, secondly, explore the influence of attachment traits and separation/loss events in relation to the role of the SEEKING and PANIC/GRIEF systems in separation distress. To my knowledge, this study is the first to attempt to pharmacologically induce in human subjects the ‘despair’ and ‘protest’ behaviours seen in various other mammal species. The sample comprised participants who had personal experience of psychoanalysis or psychotherapy, were not clinically depressed, and did not display higher than normal PA and NA, SEEKING and PANIC/GRIEF scores at baseline, compared to published norms. There was some indication that participants displayed higher avoidant and anxious scores on the ECR at baseline, but this was in comparison to one unmatched sample.
Several important issues to remember in relation to the discussion of the results is that this was an exploratory study, the psychological effects that I sought to identify were very subtle (since minimal once-off dosages were used), and the sample size was small. Moreover, given that the study lacked statistical power, no definitive conclusions could be drawn from psychometric results in isolation; the results were therefore interpreted with corroborating evidence from the qualitative data.

Essentially, the results of this study were mixed. Although the effects of the medications on dopaminergic- and opioidergic-related affects in participants was similar to those documented in other mammals, these effects were not demonstrated consistently across the whole sample. Some results were significant in the direction of predicted effects, with corroborating qualitative evidence, some were significant in the opposite direction to predicted effects, while other predictions failed to reach significance. In some instances, there was only limited qualitative support (from the psychological probes data) for predicted outcomes.

The results of each hypothesis will be discussed in relation to confirmatory evidence - where there was any at all - in support of the central claims of the study, along with various methodological, pharmacological and psychological factors that could have accounted for non-significant and inconsistent findings.

**Increased SEEKING.** In the preclinical literature, an activated SEEKING system produces an increase in exploratory activity characterised by heightened motor behaviour, motivation, energy and curiosity (Panksepp, 1998) and is generally thought to be experienced as rewarding (Alcaro & Panksepp, 2011). Therefore, the *first* hypothesis of the study was that administering Madopar (a D1/D2 agonist) would produce such increased SEEKING behaviours and improve PA and mood in a human sample. Results of the psychometric analyses showed that all predictions about Madopar were not met. Contrary to predictions, Madopar significantly reduced SEEKING and PA and had no significant effect on mood. However,
contrast to the quantitative psychometric results, the qualitative psychological probes revealed some patterns of response that were in keeping with the anticipated effects of a stimulated SEEKING system. Half of the participants reported feeling ‘positively stimulated’ -- described variously as ‘euphoric’, ‘upbeat’, ‘optimistic’, ‘happy’ and ‘high’ -- and both groups of coders were in complete agreement in this respect. Madopar had a significantly positive effect on how participants felt when recalling their ‘memories of loss’, compared to Placebo, reporting feeling less sadness and pain associated with their loss. Nine participants reported that they felt an increase in SEEKING when asked about this during the ‘directed probes’. I was thus able to qualitatively demonstrate that a stimulated SEEKING system triggered positive feelings and that it was able to reduce the sadness associated with experiences of loss, but this only happened in half the sample. In sharp contrast, the other half experienced psychobehavioural effects contrary to expectations. These participants reported feeling ‘negatively stimulated’ -- described variously as ‘anxious’, ‘detached’, ‘isolated’ and ‘sad’ -- and found the experience of a stimulated SEEKING system stimulating in an unpleasant and distressing way. These participants also frequently reported experiencing side-effects on Madopar, such as elevated heart rate, feeling jittery, shaky and nausea. The cumulative effect of negative psychobehavioural and physical effects could have contributed towards reduced SEEKING and PA scores. Moreover, the descriptive data showed that SEEKING and PA were in fact reduced by all medications, not only Madopar. This trend will be discussed in greater detail in a later section.

**Decreased SEEKING.** A pharmacologically deactivated or damaged SEEKING system leads to reduced motivation in animals, who express no eagerness to engage in any activity (Stellar & Stellar, 1985). Thus, the second hypothesis of the study was that Haloperidol (a D2 antagonist) would decrease SEEKING and worsen NA and mood in a human sample. Unlike Madopar which produced contradictory results, both the psychometric data and the
psychological probes yielded confirmatory results, more in keeping with predictions. Haloperidol significantly reduced SEEKING as reflected by reduced SEEKING scores on the ANPS. Although not significant, Haloperidol worsened mood as reflected by increased MDI scores in eight of the 16 participants. Haloperidol did not increase NA as expected, but it significantly reduced PA from baseline ($t(13) = 2.47, p = .028, d = 0.84$) in 11 participants. Many of the positive items on the PANAS scale, such as, ‘interested’, ‘excited’, ‘enthusiastic’, ‘alert’, ‘attentive’ and ‘active’ are typically descriptive of the construct of SEEKING. Since Haloperidol significantly reduced SEEKING, it is reasonable that PA would also be significantly reduced. The psychological probes provided support for the findings from the psychometric analysis. Specifically, on the ‘directed probes’, eight participants reported that they felt a decrease in SEEKING, in keeping with the statistically significant reduction in SEEKING on the ANPS. Two commonly reported affective responses to Haloperidol were lowered drive (loss of motivation, energy and interest) and detachment, which are highly typical of decreased SEEKING and low mood. On the ‘memories of loss’, although there was no statistically significant change in emotional intensity when participants were recalling their episodes of loss on Haloperidol, the majority of participants qualitatively described that they felt emotionally numb when thinking about their losses, which is not incompatible with feelings of low drive and detachment. I was thus able to demonstrate that a dampened SEEKING system did produce several depressive affects in humans akin to mammalian ‘despair’ behaviours - such as anergia, amotivation and low mood and that PA was significantly reduced.

**Decreased PANIC.** Being close to others generally feels good and it is a need we are said to share with other animals. The PANIC/GRIEF system promotes positive social bonding and it has been demonstrated repeatedly that opioids reduce separation-distress in other mammals (Panksepp & Biven, 2012). Therefore, the third hypothesis of the study was that Morphine (a µ-opioid agonist) would reduce PANIC/GRIEF and improve affective valence
and mood in a human sample. The results were somewhat mixed. In keeping with predictions, Morphine significantly reduced PANIC/GRIEF on the ANPS and even though the following association did not reach statistical significance, mood was improved in 10 participants, as reflected by reduced MDI scores on Morphine. There was evidence from the psychological probes data in support of the psychometrically significant reduction in PANIC/GRIEF and of the descriptive improvement in mood. Specifically, on ‘directed probes’, eight participants reported a decrease in PANIC/GRIEF. One of the prominent affects that were identified on Morphine was feeling ‘relaxed’. Participants reported feeling calm, subdued, mellow etc., in keeping with findings from other researchers such as O’Neill et al. (2000), who showed that their healthy subjects experienced increases in ‘subjective calmness’ on doses of Morphine equivalent to those used in the present study. Another prominent affect was a ‘muted sense of pain/detachment’. Here participants described feeling detached from their memories, but more importantly, that the pain associated with their loss was reduced or muted. Both affects are consistent with reduced PANIC/GRIEF and indicative of some improvement in mood. Furthermore, Morphine was shown to have a significant effect on change in emotional intensity when participants recalled their ‘memories of loss’, compared to Placebo, and the nature of this change was in keeping with the predicted effects of Morphine in that participants generally described feeling removed from the memory or emotion connected to it. In this sense, their PANIC/GRIEF on the Morphine recall was reduced compared to their baseline recall in that they found it difficult to access the pain associated with the loss. I was thus able to discern some evidence that a dampened PANIC/GRIEF system lead to an increase in the expression of feelings of contentment, relaxation, happiness and reduced concern and that the mental pain associated with previous loss was reduced.
With respect to PA, results were inconsistent with predictions. Morphine significantly reduced PA\(^5\). Three possible reasons could have contributed towards this finding. Firstly, as previously mentioned, the euphoric effects of \(\mu\)-opioid agonists, especially in subjects with limited previous exposure to exogenous opioids, are not consistently reported in the literature. According to Ribeiro, Kennedy, Smith, Stohler, and Zubieta (2005), it is not typical for opioid users to experience euphoric effects initially, reporting instead predominantly negative experiences often accompanied by nausea. It is generally only after continual use that the euphoric effects are experienced. Furthermore, Zacny, Lichtor, Zaragoza, and de Wit (1992) argue that \(\mu\)-opioid agonists have a biphasic effect on mood. They found that even though their subjects initially reported increases in ‘liking’ at time of dosing, fentanyl (a \(\mu\)-opioid agonist), did not increase ratings on psychometric measures of drug-induced euphoria several hours later. Other properties of the drugs such as its \(\mu\)-receptor affinity, how it was administered, the dose and genetic variations of the opioid system, could also have played a role (Levran, Yuferov, & Kreek, 2012). For instance, intravenous opioid administration produces greater euphoric effects than oral administration (Marsch et al., 2001). Nummenmaa and Tuominen (2017) conclude that although opioid agonists may produce pleasurable effects, further research is needed to establish the particular conditions under which opioid agonists actually elicit subjectively felt pleasure or euphoria. Secondly, as previously mentioned, the positive items on the PANAS scale correspond quite strongly with the construct of SEEKING. A post-hoc analysis revealed that there was a significant difference between baseline SEEKING and SEEKING after Morphine, \(t(15) = 4.95, p < .001, d = 1.82\). This significant reduction in SEEKING on Morphine could have accounted for the significant reduction in PA. Thirdly, it is not unusual for patients on chronic opioid medication to be less emotionally responsive.

\(^5\)Morphine did reduce NA from the baseline mean of 13.19 to a post-Morphine mean of 11.88, which is keeping with its predicted effects.
Johnson and Mosri (2016) describe these patient’s thinking and feelings as ‘autistic’ (p.3) to the extent that their relatedness to and need for human interaction is reduced. This is consistent with findings in the pre-clinical literature that Morphine reduces the need to seek out social contact (Nelson & Panksepp, 1998). Although participants in the current study only received a once-off dose of Morphine, it is still noteworthy that there was poor agreement between coders A and B with respect to feeling ‘Connected’, one of the prominent affects initially identified on Morphine. Coders A had originally identified this affect in eight participants, but coders B only identified it in five of the eight identified by coders A. The following description from a participant on Morphine is illustrative and points to a decrease in the desire to relate/interact with others: “Towards evening I was struck by a feeling of being very unenthused. Surprising in the circumstances because there was interesting live music, but I had no interest or wish to participate. I was noticeably bland.”

Lastly, a more general point on the role of opioids in social behaviour is that although there are numerous studies confirming this association (Nelson & Panksepp, 1998), negative reports are not uncommon, and the discrepancy of results could be due to several factors, one of them being that the administration of agonists and antagonists affects multiple opioid systems and peptides (Mansour, Watson, & Akil, 1995).

**Increased PANIC/GRIEF.** A decrease in µ-opioids is thought to lead to feelings of anhedonia, sadness, reduced PA, decreased feelings of social connection and intensified responses to social stress (Zellner et al., 2011). The *fourth* hypothesis of this study thus predicted that Naltrexone, (a µ-opioid antagonist) would increase PANIC/GRIEF and worsen affective valence and mood. Few of the predictions about Naltrexone were confirmed. PANIC/GRIEF was significantly reduced, and not increased as predicted, and NA was also not significantly worsened. Naltrexone increased PANIC/GRIEF in just five participants and increased NA in six participants. The only finding in keeping with predictions was that there
was a trend towards significance for Naltrexone to worsen mood as measured by the MDI.

The psychological probes data mirrored the psychometric findings, confirming that Naltrexone did not increase PANIC/GRIEF as expected. Throughout the psychological probes for Naltrexone, there was little indication of increased feelings of sadness relating to loneliness, social isolation, longing for significant others or rejection; the essence of what comprises an increase in PANIC/GRIEF. Only for ‘memories of loss’ did two participants report an increase in sadness, but mostly participants described difficulty connecting with their memories. Moreover, the only prominent affect that both coders A and B agreed upon was that of feeling ‘detached’; participants described feeling detached from the affect associated with their memories of loss and of feeling removed. An increase in PANIC/GRIEF as measured by the ANPS is strongly centred on increases in feelings of sadness relating to intimate others and social loss or isolation. If participants felt affectively disconnected, it is not likely that they would have readily agreed to statements affirming any increase in psychological pain relating to separation from or loss of intimate relationships. To confirm this, I re-examined each participant’s response to the seven statements on the ANPS indicating an increase in PANIC/GRIEF. Of the total 112 responses to statements indicating an increase in PANIC/GRIEF, only 17 responses indicated ‘agree’; the majority of responses indicated ‘disagree’ or ‘strongly disagree’ to statements describing an increase in PANIC/GRIEF. To illustrate: only three participants agreed with the statement “I often feel sad”; no participants agreed with the statement “I often have the feeling that I am going to cry”; two participants agreed with the statement “I often think about people I have loved who are no longer with me”; three participants agreed with the statement “I tend to think about losing loved ones often” and so forth. This not only explains the lack of increase in PANIC/GRIEF but also explains the significant decrease in PANIC/GRIEF on the ANPS. This pattern of response on the ANPS was likewise reflected in the psychological probes.
data. On ‘directed probes’ nine participants indicated ‘no change’ in increased feelings of PANIC/GRIEF. Feelings of disconnection on Naltrexone are commonly reported. For instance, Inagaki and colleagues (2016) and Inagaki (2018) found that subjects felt socially disconnected on Naltrexone. Chelnokova et al. (2016) reported that Naltrexone reduced the time that their participants spent fixating on facial images, indicating that opioid antagonism led to people paying less attention to the face and eyes and thereby gathering less socially relevant information. Jamner and Leigh (1999) found that female participants who were administered Naltrexone felt a decrease in pleasure in relation to social interactions and spent a greater time alone. My finding that participants felt affectively disconnected is thus in keeping with this research. Disconnectedness is not synonymous with loss, but it is of course the opposite of feeling connected.

Furthermore, the question of whether dysphoric or depressive symptoms are associated with the use of Naltrexone remains controversial. Several studies have reported such side-effects (Crowley et al., 1985; Hollister et al., 1981; Mendelson et al., 1978). For instance, Depue and Morrone-Strupinsky (2005) found that blocking opioids diminishes warmth and affection in women who were shown an affiliative type of film clip. Schweiger et al. (2014) showed that women reported a decrease in feelings such as cosiness and being liked in a game of trust after taking Naltrexone. Other studies however (Dean et al., 2006; Miotto et al., 2002) have not confirmed these claims. For instance, in the Van Steenbergen, Weissman, Stein, Malcolm-Smith, and van Honk (2017) study, a dose of 50mg Naltrexone (a dose equivalent to the one used in the present study) found no significant effects on negative or positive affect as measured by the PANAS. The results of this study, it would seem, are more in keeping with the former view, for two reasons. Firstly, there was a trend towards significance between Naltrexone and mood as reflected by higher MDI scores in half of the participants. Secondly, although Naltrexone did not significantly increase NA as expected,
this finding was more understandable when I re-examined each participant’s responses to the
ten NA items on the PANAS. No participants felt ‘ashamed’ and for the following affects
‘upset’, ‘guilty’, ‘scared’, and ‘afraid’, only two participants in each case indicated feeling ‘a
little’ of this type of affect. This is reasonable, given that these types of affects are not
typically associated with Naltrexone. In light of this, I performed a post-hoc analysis of
Naltrexone’s effects on PA and found a statistically significant result, $z = -3.53$, $p < .001$, $r$
= 0.883; Naltrexone reduced PA in all 16 subjects. Therefore, although Naltrexone did not
increase PANIC/GRIEF, there was evidence to show that a stimulated PANIC/GRIEF system
produced depressive affects, as reflected in increased depression scores, significant
reductions in PA and feelings of social/affective disconnection.

Other factors to consider which could have impacted these results are that although
Naltrexone has the highest sensitivity for mu-opioids, the possibility of kappa antagonism,
which is known to produce dysphoric responses in humans could not be excluded
(Ranganathan et al., 2012); Naltrexone’s effects could be specific to certain types of stimuli
and varying effects depending on dosing regiments, that is, chronic versus once-off (Wardle,
Bershad, & de Wit, 2016).

**Attachment and opioids.** With regard to the relative effects of Morphine versus
Naltrexone on the SAAM attachment measure, I found that avoidance on Morphine was
significantly lower than avoidance on Naltrexone. This result was in keeping with
Naltrexone’s general effects in that feeling ‘detached’ was a prominent affect which could
have made participants feel more avoidant. Although there was no significant difference on
security between the opioid-related medications, security scores on Morphine were greater
compared to Naltrexone in 10 participants. This too was consistent with the emotional
effects of Morphine. Participants felt ‘relaxed’ and had ‘a muted sense of pain/sadness’,
which could have contributed towards a stronger sense of security. Lastly, there was no
significant difference on anxiety between the opioid-based medications; anxiety was only lower on Morphine compared to Naltrexone in six of the 16 participants. One possible reason for this could be that the study sample was found to be significantly more anxious when compared to an unmatched data set.

**Despair as the normal prototype for depression.** A shutdown of the SEEKING system is said to constitute the despair phase of the separation distress response and since the despair phase is hypothesised to be the normal prototype for depression, I investigated whether SEEKING, mood and affective valence would be differentially affected in participants with high depression scores vs those with low depression scores. The sample was split into High and Low depression groups based on MDI scores, with the two groups representing High and Low ‘despair’ respectively. The *fifth* hypothesis of the study predicted that the two groups would differ in their responses to the psychometric measures and psychological probes on the Dopamine-related medications. Even though there were no statistically significant differences between the groups on Madopar, descriptively, the reduction in PA and the increase in NA and MDI scores from baseline was in each instance comparatively greater in the High ‘despair’ group. This is probably due to the interesting trend that the majority of participants in the High ‘despair’ group described their experience on Madopar as ‘negatively stimulating’, while the majority of participants in the Low ‘despair’ group described their experience as ‘positively stimulating’. On Haloperidol, however, the Low ‘despair’ group had significantly reduced SEEKING and PA and higher depression scores, compared to the High ‘despair’ group. Taken together, these two findings may suggest that Low ‘despair’ participants are less familiar with depressive feelings and therefore show greater sensitivity to the up and down regulating effects of Madopar and Haloperidol. The psychological probes data provided some corroborating evidence for these findings. The most notable difference between the group’s responses to Haloperidol was that
considerably more participants in the High ‘despair’ group felt ‘detached’ (six participants in this group compared to two in the Low ‘despair’ group), which could explain why they would not necessarily indicate any significant alterations in their affect. Furthermore, twice as many participants in the Low ‘despair’ group compared to the High ‘despair’ group experienced a ‘low drive’ on Haloperidol which could account for the reduced SEEKING and PA and the higher MDI scores in this group. A more compelling finding was that there was a significant association on the ‘directed probes’ between SEEKING and both DA medications in the Low ‘despair’ group; a higher proportion of participants in this group reported an increase in SEEKING when on Madopar and a decrease in SEEKING when on Haloperidol. With respect to ‘memories of loss’, there was a significant association between change in emotional intensity and Madopar, when compared to Placebo in the Low ‘despair’ group. Of the six participants who experienced a change, five described feeling either less emotional pain or more positive when re-experiencing their memories of loss, which was in keeping with five participants in this group feeling ‘positively stimulated’ on Madopar. Thus, the Low ‘despair’ group confirmed predictions that high vs low depression scores would differentially influence SEEKING, affect and mood, albeit for Haloperidol only. More importantly, the nature and direction of this change was not only in keeping with the study’s hypothesis about the anticipated effects of a dopamine antagonist, but for the first time, I was also able to demonstrate, with significance, in a subset of participants with Low ‘despair’, a subjective increase in SEEKING, and an improvement in PA and mood (that is, feeling ‘positively stimulated’ and experiencing less emotional pain) on Madopar, which was more in line with the predictions of the study’s first hypothesis. In short, participants with lower depression scores had opioid systems that behaved as expected and those with higher depression scores did not. This broadly suggests that depressed affect is associated with opioid dysregulation.
Although the effects of the opioid medications on the split MDI groups were not included in the study’s original predictions, an interesting descriptive finding mentioned previously was that the High-Despair group appeared relatively more responsive to the opioid antagonist compared to the Low-Despair group. What stood out in particular was the effect of Naltrexone on SEEKING. A post-hoc analysis revealed that the difference in SEEKING between the groups was significant, \( t(14) = 2.16, p = .049, d = 1.08 \). What these results tentatively illustrate is the mechanism of pathological depression – as conceptualised in this thesis – in action. To reiterate, in affective terms, major depression is understood as a disorder characterised by an overactive PANIC/GRIEF system and underactive SEEKING system (Panksepp, 2004). I was able to show that the stimulation of PANIC/GRIEF in participants with higher depression scores, led to a comparatively larger reduction in SEEKING, compared to those participants with lower depression scores. Thus, prolonged social loss, as reflected by a stimulated PANIC/GRIEF system, diminished SEEKING to a greater extent in those with higher despair.

**Protest and avoidant attachment.** An overactive PANIC/GRIEF system putatively constitutes the protest phase of the separation distress model, and since protest is in response to separation from an attachment figure, I investigated whether PANIC/GRIEF, mood and affective valence would be differentially affected in participants who were more or less avoidant or more or less anxious in their attachment styles to romantic partners. The sample was split into High and Low avoidance/anxiety groups based on ECR scores, with the two groups representing High and Low ‘protest’ respectively. The sixth hypothesis of the study predicted that the two groups would differ in their responses to the psychometric measures and psychological probes on the Opioid-based medications. Although the Low and High-Avoidance groups did not show any statistically significant differences for PANIC/GRIEF, PA or mood on the opioid-based medications, there was a significant difference for NA, with
the Low-Avoidance group experiencing a significantly larger reduction in NA on Morphine and Naltrexone. Moreover, descriptively, PANIC/GRIEF scores were reduced to a greater extent from baseline in the Low-Avoidance group compared to the High-Avoidance group and MDI scores were reduced for the Low-Avoidance group but increased for the High-Avoidance on Morphine. There was some support for these psychometric findings in the psychological probes data. The following are statements from participants in the Low-Avoidance group on Morphine: “I feel less negative emotion than when I last described”, “I feel much more a sense of pleasure in relatedness to others”, “It turned into a slight…don’t want to say euphoria because that is too strong, but maybe a slight happiness”, “I do feel relaxed and comfortable in terms of people that are close to me and people that I, you know, interacting with people”, “What is coming to mind is enjoyable events I had with her, not the actual split. This is unusual” and “The mental imagery is more positive that what it would normally be”. Taken together, these results provide some evidence that participants with lower avoidance scores, and hence a more secure sense of dependence on others, experienced less PANIC/GRIEF and NA and an improvement in mood on Morphine, compared to participants with higher avoidance scores. This is in keeping with the earlier finding that avoidance on Morphine was significantly less than avoidance on Naltrexone on the SAAM questionnaire for the whole sample, which highlights a degree of consistency between the two measures of attachment. Moreover, the Low-Avoidance group had significantly higher SEEKING scores at baseline compared to the High-Avoidance group which is also consistent with the overall positive experience of this group on Morphine. Maccallum and Bryant (2018) argue that high avoidance attachment essentially results in a shutdown of attachment and social withdrawal, which could have contributed to the comparatively lower baseline SEEKING scores for the High-Avoidance group. High attachment avoidance has also been associated with lower responsivity of brain circuits involved in emotional processing and low
MOR availability in regions linked to social distress and social interaction (Nummenmaa et al., 2015). This study’s findings are consistent with this view in that I found that participants who were relatively more avoidant, that is, those with High ‘protest’, were comparatively less responsive to the associated feelings of a Morphine-related decrease in PANIC/GRIEF such as feeling bonded and attached. Several statements from the psychological probes data of participants who were relatively more avoidant point to this kind of emotional detachment and an unwillingness/inability to engage with memories of personal loss: “It feels peripheral at the moment; I’m unable to intensely experience that now”, “I can acknowledge the feelings but not experience the feelings”, “My recollection of it now is a feeling of loneliness; different than usual”, “I can remember the feeling, but I’m not feeling the feeling”, “It’s less of an intense emotional experience”, “I don’t feel emotionally attached to that event, or I don’t feel a link to the emotions I would have felt” and “I was feeling unconfident, a little socially embarrassed, which is unusual for me”. Therefore, there was some qualitative and descriptive evidence to show that those participants with higher avoidance/higher protest were less responsive to the associated feelings of a dampened PANIC/GRIEF system, reflected in comparatively higher PANIC/GRIEF and MDI scores and a smaller reduction in NA.

**Protest and anxious attachment.** There were no significant differences between the Low and High-Anxiety groups for PANIC/GRIEF, affect or mood on the opioid-based medications. There were however two trends towards significance. Firstly, the Low-Anxiety group reported a comparatively greater decrease in PANIC/GRIEF on the ANPS on Morphine. There was evidence of this psychometric trend in the psychological probes data also, as reflected in the statements of participants from the Low-Anxiety group: “I have an overall positive affect; I feel happy”, “I’m feeling strangely calm”, “It was easier to engage with how I felt; I felt calm and relaxed”, “Definitely just more content”, and “I feel content
and energised.” The second trend was for the High-Anxiety group, who on ‘directed probes’, reported a comparatively greater decrease in PANIC/GRIEF on Morphine. There was once again support for this trend in the psychological probes data in the statements of participants from the High-Anxiety group: “It’s kind of a warm comfort, almost a slightly numb sensation”, “I don’t feel worried or panicky at all”, “There is no sense of panic”, “I’m not feeling any stress”, “I’m feeling pretty calm” and “Feeling quite sort of mellow”. Although both groups experienced a reduction in PANIC/GRIEF on Morphine, as expected, these trends were at odds. On ‘directed probes’, the High-Anxiety group were clearly experiencing the anxiety-alleviating effects of Morphine to a greater extent than the Low-Anxiety group, but this pattern was reversed on the ANPS; here the Low-Anxiety group experienced the greater reduction in PANIC/GREIF. One reason could be the lack of significant association between the two measures of PANIC/GRIEF (ANPS and ‘directed probes’), to be discussed in greater detail in a later section. Another possible explanation as to why these trends were antithetical and why I did not find any clear significant differences between the two anxiety groups on both opioid-based medications is that Nummenmaa et al. (2015) reported that individual differences in attachment anxiety, unlike attachment avoidance, were not influenced by endogenous MOR availability and that avoidant and anxious attachment may be supported by distinct pathways. Along these lines, this study’s results showed that unlike avoidant attachment, where differential patterns of response between low vs high avoidance were discernible, both opioid medications had comparatively little differential between-group effects on depressive affect and NA in relation to Low vs High anxiety. The Low and High-Anxiety groups mean MDI and NA scores post Morphine were almost identical. The same applied to Naltrexone. Furthermore, the mean MDI scores for both groups on Morphine were very close to their respective baseline means, pointing to a possible lack of association between a dampened PANIC/GRIEF system, Low vs High-anxiety and depression scores.
The only notable difference between the groups was for PA. The mean PA score post Morphine was greater for the High-Anxiety group compared to the Low-Anxiety group, indicating that a dampened PANIC/GRIEF system was possibly associated with a greater increase in PA for those with higher anxiety, which is a reasonable outcome.

These findings on avoidant and anxious attachment, although tentative and exploratory and from a small subset of participants, begin to shed some insight into the largely unexplored relationship between depressive affect, attachment and loss. Although lacking psychometric significance, qualitatively and descriptively, there was some evidence to show that dampening the PANIC/GRIEF system led to those participants with higher avoidance to experience less reduction in their PANIC/GRIEF and NA, and an increase in depressive affect. There were thus some identifiable differences between Low and High ‘protest’, as measured by the avoidance subscale, and depressive and NA. The results for anxious attachment were mixed. There were no recognizable differences between Low and High ‘protest’, as measured by the anxiety subscale, and depressive affect and NA, but there were descriptive differences between Low and High-Anxiety for PA. In light of these results, an interesting theoretical consideration is that the role of the PANIC/GRIEF system in depression could relate more to avoidance and social withdrawal rather than anxiety, and possibly even to a certain subtype of depression. In his paper ‘Affective neuroscience of the emotional BrainMind’, Panksepp (2010) introduced the idea of relating various subtypes of depression to the different basic emotion systems. Furthermore, since a relationship between attachment style and the opioid system has previously been established (Nummenmaa et al., 2015) and is suggested by this study’s findings, the use of opioid medications as a ‘fill-in’ for secure attachment in avoidant individuals would be an interesting area for future research.

**Two general trends in the results.** Firstly, and as previously mentioned, SEEKING and PA were reduced from baseline by all the medications in the whole sample. Possible
reasons why this occurred in the case of Madopar have already been discussed. In the case of Haloperidol, a reduction in SEEKING was in keeping with its predicted effects as a DA antagonist. Its effect on PA has previously been addressed, but in addition, Haloperidol has been shown to have a negative impact on contentment in healthy subjects (Saeedi et al., 2006), which would also contribute to the decrease in PA and worsening of mood.

With regards to Naltrexone, as previously discussed, the existing evidence is inconsistent. There are studies that have shown that dysphoria can be a side effect of Naltrexone (Hollister et al., 1981), which could explain why Naltrexone reduced SEEKING and PA. There is some degree of support for this view from the current study in that some participants experienced negative psychobehavioural effects on Naltrexone akin to dysphoria, such as disconnected, reluctant to engage, feeling subdued, difficulty concentrating, reduced interest and anxiety. Although evidence is once again limited, there is another view that normal subjects may be at greater risk of having dysphoric reactions (Miotto et al., 2002) or that subjects who are under substantial physical or psychological stress may experience dysphoric symptoms on Naltrexone (Malcolm, O'Neil, Von, & Dickerson, 1987). Both possibilities could have played a role in the current study to explain Naltrexone’s effects on SEEKING and PA, since the study’s sample was normal and found to be significantly more anxious on the ECR. The latter statement, however, must be interpreted with caution since this finding was based on a comparison to one unmatched data set.

In the case of Morphine, the interaction of opioids with other neurotransmitters is complex. Opioid agonists are known to effect DA release, reuptake and metabolism in the striatum and substantia nigra (Kream, Stefano, & Ptáček, 2010). Morphine is associated with increased DA neuronal firing in the VTA, activation of mesolimbic pathways, and an increase in extracellular DA in the NAc (DiChiara, Acquas, & Carboni, 1990). These interactions could possibly account for Morphine’s effect on SEEKING. Moreover, and as previously discussed,
although studies on opioid-naïve subjects have reported increases in euphoria and pleasure following administration of μ-receptor agonists (Riley et al., 2010; Zacny & Gutierrez, 2009), several studies have failed to corroborate such findings. Ipser et al. (2013) found that although the partial μ-opioid agonist, buprenorphine, decreased fear recognition in normal subjects, it had no effect on mood. Tedeschi, Smith, and Richens (1984) also reported no mood effects on the partial μ-opioid receptor agonist, Meptazinol. In the classic study of Lasagana, Felsinger, and Beecher (1955), the authors reported that former addicts were more likely to experience the positive effects of opioids compared to subjects who were administered opioids for the first time, and of the 20 non-users in their study, only two indicated that they would be willing to repeat the study. Those subjects who were naïve to opioid use reported that they felt sedated, mentally clouded and ill. In the current study, there were several participants who similarly reported feeling tired and fuzzy/foggy on Morphine. It is possible that the sedative effects of Morphine, coupled with one of its prominent affects, namely, feeling ‘detached’, would not likely have engendered increased feelings of SEEKING. A possible explanation as to why Morphine decreased PA could, as previously discussed, lie in the items that constitute PA in the PANAS. Specifically, items such as ‘interested’, ‘excited’, ‘strong’, ‘enthusiastic’, ‘proud’, ‘alert’, ‘inspired’, ‘determined’, ‘attentive’, and ‘active’ are strongly aligned with the construct of SEEKING. I re-examined each participant’s PA questionnaire on Morphine and noted that 11 participants indicated a lower score (compared to baseline) on the following items: ‘interested’, ‘excited’, ‘enthusiastic’, ‘alert’, ‘inspired’, ‘determined’, ‘attentive’, and ‘active’. Thus, the significant decrease in SEEKING together with the observed sedatory effects of Morphine, could have accounted for the significant reduction in PA.

Lastly, SEEKING was also significantly reduced by Placebo, which is not an entirely unexpected finding since placebo effects are thought to rely on the release of endogenous
opioids (Zubieta et al., 2005), and these effects have been shown to be associated with opposite responses of DA and opioid activity (Scott et al., 2008).

Secondly, except in the case of Haloperidol, where there was a trend towards significance, a result that was common to the other three medications was that there was no statistically significant relationship between the psychometric definitions of SEEKING and PANIC/GRIEF, as measured by the ANPS, and their ‘directed probes’ counterparts. On Madopar, 14 participants reported a decrease in SEEKING on the ANPS, whereas on ‘directed probes’, nine reported an increase in SEEKING, resulting in the lack of correlation between the two measures. The formal psychometric nature of the one measure compared to the qualitative nature of the other could have contributed towards the differential responses from participants. On the ‘directed probes’, increased SEEKING was explained to participants to mean: ‘Wanting to find or discover something; searching or looking for something; feeling inquisitive about or interested in something; actively looking forward to or anticipating something; being positive; being hopeful.’ On the ANPS, high SEEKING was measured by 7 statements: “Almost any little problem or puzzle stimulates my interest”, “Seeking an answer is as enjoyable as finding the solution”, “I enjoy anticipating and working towards a goal almost as much as achieving it”, “I really enjoy looking forward to new experiences”, “My curiosity sometimes drives me to do things that others might consider a waste of time”, “Whenever I am in a new place I always like to explore the area and get a better feel for my surroundings” and “I often feel I could accomplish almost anything” (Davis & Panksepp, 2011). The ‘directed probes’ version was relatively more expansive and sanguine, especially with the inclusion of feeling ‘positive’ and ‘hopeful’, compared to the ANPS with its stronger focus on concrete and practical examples of activities. During the ‘directed probes’, participants were encouraged to explore the construct of SEEKING more widely and some of the qualitative descriptives that they used were: ‘happy’, ‘euphoric’, ‘upbeat’, ‘optimistic’, ‘confident’, ‘bold’, and ‘engaged’.
These nuanced affects would not necessarily be captured by the SEEKING questions on the ANPS. Also, specific references to increased curiosity, anticipation or interest were rarely made in relation to the positive feelings experienced on Madopar, which could possibly explain why participants were less likely to report an increase in SEEKING on the ANPS compared to ‘directed probes’.

The two measures of PANIC/GRIEF were likewise not consistent with one another. On Morphine, more participants reported a decrease in PANIC/GRIEF on the ANPS compared to the ‘directed probes’, where eight participants reported no change in PANIC/GRIEF. A decrease in PANIC/GRIEF on ‘directed probes’ was described to participants as: “Feelings of safety and security; warm fuzzy feelings, like being loved and cared about; the feeling of being bonded or attached; and the associated feelings of being confident about the reliability of intimate others and durability of relationships.” On the ANPS, a decrease in PANIC/GRIEF was measured by the following seven questions: “I seem to be affected very little by personal rejection”; “I rarely become sad”; “I never become homesick”; “It does not particularly sadden me when friends or family members are disapproving of me”; “I rarely have the feeling that I am close to tears”; “I rarely think about people or relationships I have lost” and “It would not bother me to spend the holidays away from family and friends” (Davis & Panksepp, 2011). The ‘directed probes’ definition of decreased PANIC/GRIEF had a relatively stronger emphasis on feelings of being loved by and bonded to intimate others. As previously mentioned, feeling ‘connected’, which specifically referred to an increased desire to be with loved ones, was the third prominent affect identified by coders A. However, coders B were not in strong agreement with coders A (only 62.5%) as to the prominence of this affect, identifying it in only six participants. This could possibly explain why half of the participants reported no change in PANIC/GRIEF on ‘directed probes’, with its stronger emphasis on feelings of attachment, because those feelings were not as prominent as originally thought. For Naltrexone,
although the direction of change in PANIC/GRIEF reported by participants was contrary to predictions, the two measures were once again inconsistent. Eleven participants reported a decrease in PANIC/GRIEF on the ANPS, while nine participants reported no change in PANIC/GRIEF on ‘directed probes’. This issue has previously been discussed in an earlier section but is reiterated now for contextuality. On the ANPS, an increase in PANIC/GRIEF was measured by the following seven questions: “I often feel sad”; “I often have the feeling that I am going to cry”; “I often feel lonely”; “I often think about people I have loved who are no longer with me”; “I tend to think about losing loved ones often”; “I frequently feel downhearted when I cannot be with my friends or loved ones”; “I am a person who strongly feels the pain from my personal losses”. The prominent affect for Naltrexone was that participants felt emotionally detached/disconnected and this led to responses of ‘disagree’ or ‘strongly disagree’ to many of the above ANPS statements, given their strong emphasis on feelings about intimate relationships and connections. As mentioned already, this is potentially important for the simple reason that ‘detachment’ is the opposite of ‘attachment’. Participants in general rarely made references to feelings of increased psychological pain as expected. What was more commonly described was an absence of feeling – an emotional numbness. These reasons would have accounted for the decrease in PANIC/GRIEF scores on the ANPS. On the ‘directed probes’, an increase in PANIC/GRIEF was described as an increase in the following types of feelings: ‘Mental suffering or mental pain of the kind caused by the prospect or experience of separation, loss, or rejection; or the ensuing mental anguish, torment or distress caused by separation, loss, or rejection.’ The emotional detachment/numbness and the absence of NA would similarly have accounted for participants reporting no change in PANIC/GRIEF on ‘directed probes’, with its strong emphasis on increases in mental anguish/suffering.

Two further points about the lack of correlation between the two measures is that on the ‘directed probes’, participants had an option of indicating that they felt no change in
SEEKING or PANIC/GRIEF, whereas this was not an option on the ANPS. Secondly, the ANPS is a personality scale and to my knowledge has not been used previously to measure changes in state. Thus, the extent to which the ANPS was in fact measuring changes in personality, or whether changes in traits can occur following once-off pharmacological manipulation, is questionable.

Either way, over and above the lack of correlation between the two measures, the results of either measure independently were variable and not always consistent with predictions. To illustrate: The results of the ‘directed probes’ were consistent with the predictions about the dopamine-based medications, but not the opioid-based medications. The results of the ANPS were consistent with the dopamine antagonist and opioid agonist, but not the dopamine agonist and opioid antagonist.

**Aims of the study revisited.** The critical question is thus: to what extent do these results provide confirmatory evidence for the central aims of this study?

The first aim was to explore whether a stimulated PANIC/GRIEF system and a dampened SEEKING system would lead to depressive affects that were homologous to the mammalian separation distress behaviours of ‘protest’ and ‘despair’. Although I was unable to demonstrate that a PANIC/GRIEF system stimulated by Naltrexone led to an increase in the feelings typically associated with ‘protest’, such as the panicky mental distress of separation anxiety, I was able to provide some evidence that (qualitatively and descriptively) it led to the worsening of mood, a significant reduction in PA and feelings of social and affective disconnection. There was some evidence to show that a PANIC/GRIEF system dampened by Morphine lead to an increase in the expression of feelings of contentment, relaxation, happiness and reduced concern and that the psychological pain associated with loss was reduced. Likewise, there was some evidence to show that, qualitatively, a SEEKING system dampened by Haloperidol led to a worsening of mood and PA and produced depressive affects such as
low drive, low energy, loss of motivation and interest and detachment – affects typically associated with the ‘despair’ phase of separation distress. Furthermore, when the SEEKING system was dampened in this way, participants with lower ‘despair’ had significantly reduced SEEKING and PA and higher depression scores, compared to participants with higher ‘despair’. I was also able to provide some qualitative evidence that a SEEKING system stimulated by Madopar generated positive affects and that participants re-experienced their ‘memories of loss’ in a more positive light. Moreover, a SEEKING system stimulated in this way produced a greater improvement in PA and mood in the subset of participants with lower ‘despair’ compared to those with higher ‘despair’. Lastly, I was able to show that the stimulation of PANIC/GRIEF by Naltrexone in a subset of participants with high ‘despair’ led to a comparatively larger and significant reduction in SEEKING, demonstrating that prolonged social loss diminishes SEEKING.

The second aim of this study was to investigate the role of attachment style in relation to depressive feelings and loss. The study’s findings suggested that measures of avoidant attachment rather than anxious attachment were comparatively more effective in differentiating between Low and High ‘protest’, when the PANIC/GRIEF system was dampened, and that those with higher ‘protest’ experienced comparatively more PANIC GRIEF, negative and depressive affect.

The data thus provided suggestive rather than strongly confirmatory evidence for the central aims of this study. Various factors and limitations have been considered previously as to why this would be the case. One factor however remains to be addressed which I believe greatly impacted upon results and could have accounted for much of the inconsistency in observed participant responses. I refer here to the ‘human’ element – the specific target of this study. Obtaining subjective self-reports from human beings was a unique strength of this study, but it also acted as a significant confound. In humans, unlike animals, there is much more
cortical elaboration of primary affective responses. Human consciousness is not only raw affect; human consciousness includes the cognitive elaboration of the affect to an unusually high degree. How one interprets one’s feelings at any given moment is a combination of one’s whole cognitive development in relation to the raw affect. A core affect can be interpreted/elaborated in completely different ways by different people. Imagine, for example, the different ways in which a celibate priest and an aspirant ‘jock’ might experience sexual arousal. This sort of thing was observed consistently throughout this study and illustrated particularly well by Madopar. All the participants described feeling stimulated, which was the core affect, but half experienced this arousal as positively stimulating and the other half as negatively stimulating. Morphine did not reduce the psychological pain of all participants. Some felt relaxed, described variously as ‘calm’, ‘warm’, ‘content’ and ‘happy’ while others felt detached. Likewise, some participants experienced the feeling of low drive on Haloperidol as lowered energy, motivation and interest and feeling withdrawn, while others experienced it as relaxing, comfortable, and calm. A few participants experienced feeling severely depressed on Naltrexone, while a few -- in sharp contrast -- had very pleasurable responses to Naltrexone.

Administering medications to change the quality of participant’s experience often had opposite effects on their experience of well-being via the same fundamental mechanism. The implication here is that if these opposite effects were observed with these particular medications in this study, could this not apply to all psychoactive medications? In fact, what was observed is not inconsistent with what a substantial body of literature shows. There are widely varying results about the efficacy of antidepressants. Studies have reported that only half of patients taking them respond positively and 55% will experience at least one adverse side effect (Papakostas, 2009). In a recent review of SSRIs versus placebo in patients with major depressive disorder, involving the analysis of 131 trials, Jakobsen et al. (2017) reported that although most studies did show a small benefit from this antidepressant treatment, the
‘benefit’ translated to a mere 1.29 points on the Hamilton Depression Rating Scale in the case of mild to moderate depression and 2.69 points in the case of severe depression. A 3-point difference on the HDRS has been reported as “no clinical change”, that is, it is undetectable by patient and clinician alike (Leucht et al., 2013; Moncrieff & Kirsch, 2015). Moreover, the authors found an increase in the risk of serious and several non-serious adverse events related to the use of SSRIs. A meta-analysis by Fournier et al. (2010) found that the benefit of SSRIs compared to placebo was related to the severity of depressive symptoms, that is, minimal or non-existent in mild to moderate depression and substantial in the case of severe depression. Similarly, Kirsch et al. (2008) reported that clinically significant differences between antidepressants and placebo could only be demonstrated for patients who scored more than 28 on the HDRS, that is, for those patients who were severely depressed. Additional analyses indicated that the perceived clinical efficacy among those severely depressed patients was due to them being less responsive to placebo rather than more responsive to antidepressants. Even more recently, Cipriani et al. (2018) published results from a meta-analysis of 522 trials of 21 antidepressants and placebo and found that antidepressants were more effective than placebo for the short-term treatment of depression only in patients diagnosed with moderate to severe depression.

Personalized medication has been one response to the variability of reported antidepressant effectiveness. The argument here is that different people need different types of medications based on their genotype and other biomarkers. For example, there is some evidence that polymorphisms in genes regulating the HPA axis can influence responses to antidepressant medications (Binder & Holsboer, 2006) and specific blood tests have been designed to detect elevated levels of inflammation that have been associated with poor antidepressant response (Cattaneo et al., 2016), to cite but a few. Another response from psychiatry has been to re-visit the diagnostic categories for depression. Dowrick (2009)
identifies three intellectual ‘border disputes’ about the category of depression. There are those who argue there is considerable overlap in the symptomology of depression and other mood disorders, and consequently other diagnoses are in danger of being obliterated. Some view the category as being too narrowly defined, proposing a fusion with other diagnoses and, lastly, there are those who consider the category as too broadly defined, arguing for different subtypes of depression. Considering my findings, a possible alternative account could be that the drugs only influence one aspect of the mind, namely raw affect. The other aspect of the patient, that is, their cognition, their cortex, is not fundamentally – and certainly not only – governed by neuromodulators. The cortex – which is very much larger in humans than the animals typically studied in preclinical trials, namely rodents – differs substantially in this respect from limbic and especially upper brainstem structures. It is a highly individualised memory-based structure made up of one’s individual lifetime experiences. This accounts for the way in which we interpret our feelings, and links directly to psychodynamic concepts of internal working models (Bowlby, 1969) and self-referential processing, discussed in the introduction.

These interpersonal interpretive mechanisms that process the self in relation to significant others remain pivotal to understanding depressive states. Psychodynamically, all types of distress, including separation distress, lead to the enlisting of cognitive-affective schemas which mediate the distress (Blatt & Luyten, 2009).

No drug can alter the structure of one’s memory or personality or cognition, and therefore drug therapy alone will probably never be sufficient to assist the totality of the depressive mind. In Freudian terms: one cannot treat the id alone; the ego too must be treated. The defensive structure of the mind must be taken into account.
Limitations and Future Considerations

Small sample size and insufficient power. As previously acknowledged, the small sample size was a serious limitation of the current study, generating a statistical power of only 0.59 for the whole sample analysis. The small and selective sample used in the current study prevents findings from being extrapolated, and possibly undermines the internal and external validity of this study. Furthermore, many analyses were run in relation to the small sample size and were not Bonferroni corrected. Since this was an exploratory study - an introductory and novel investigation - it was important not to miss any potential effects and findings, which could inform further research in this area. However, it is acknowledged that low-powered studies produce more false negatives and the probability that an observed effect that reaches statistical significance actually reflects a true effect, is also lowered (Button et al., 2013; Faber & Fonseca, 2014). The current small sample size is explicable to some extent for a few reasons, the first being the highly specific selection criteria. Participants had to be selected from psychological-related professions or they had to have undergone some kind of long-term psychotherapy and they had to be known to the study's consultant psychoanalyst. They had to commit to six interview sessions over an extended period of time, disclose potentially painful experiences from their past and most importantly, agree to ingest four psychoactive medications. Thus, the level of commitment required from participants was substantial. Under these circumstances, the recruitment process was highly challenging, and I was ultimately fortunate to be able to recruit 16 motivated and scientifically curious participants who remained committed throughout. Secondly, the small sample size afforded me the opportunity to investigate each participant's responses in great depth (both quantitatively and psychologically). The qualitative in-depth investigation of participant responses was an essential aspect of this study, if I was going to succeed in identifying subtle mood effects. The qualitative data that was gathered proved to be invaluable. It is based on
this data that many subtle affective responses to the medications were identified; affects that would not have been identified had I relied solely on purely psychometric measures derived from broadly defined concepts. The aforementioned points underscore the complex issue of sample size in studies of this nature. For instance, replicating this study would require that the sample size be set at \( N = 47 \) in order to achieve statistically significant power > .90. This would entail enormous recruitment challenges and data collection could prove to be significantly onerous. These are factors that would need to be addressed when considering future replication studies.

**Quasi-experiment limitations.** The most significant limitation of this type of design is the lack of randomization, which challenges the validity of the study. Another limitation is that subjects in quasi-experimental studies typically undergo interventions in the same order, which precludes blinding (Thompson & Panacek, 2006). The reader is reminded that the study’s psychoanalyst and participants were blind to the medications and the order in which the measures were administered were counterbalanced.

**Measures.** There were various methodological issues relating to the measures used in the study. Two different attachment questionnaires were administered - the ECR-R at baseline and the SAAM post-intervention - which excluded pre and post comparisons. An attachment measure that can be adapted to measure both trait and state changes would be better suited for future research. There are some shortcomings of the ANPS which could have impacted results. It has been reported that people do not differentiate well between feelings of distress and loneliness with regard to the PANIC/GRIEF system (Davis et al., 2003). Others have found the full scale to be overly long, to have a poorly defined factor structure, for some items to be poorly worded, and an overlap to exist between the FEAR and PANIC/GRIEF subscales (Barret et al., 2013; Geir, Selsbakk, Theresa, & Sigmund, 2014). Gender differences on the ANPS have been identified, with women scoring higher on the CARING,
FEAR and PANIC/GRIEF subscales (Pingault, Pouga, Grèzes, & Berthoz, 2012).

Furthermore, the ANPS is a personality measure and although it has been used in several neurobiological studies, I am not aware of the scale being used previously to measure state changes. Thus, the effectiveness of the ANPS to measure subtle changes in core affects following psychopharmacological manipulation is unknown. Furthermore, unlike ‘directed probes’ where participants had the option to indicate if they felt no change in affect, post medication, there was no equivalent option on the ANPS to indicate no effect, which was one of the reasons that these two measures lacked statistical association. In general, given the wide range of emotions elicited by the medications in this study, the use of more discriminable measures of affect is recommended for future research. For instance, positive and negative affect on the PANAS are broadly defined constructs and this measure was possibly ineffective in measuring the more subtle emotional affects produced by the medications. The design of new measures of affect specifically based on current results is worthy of future consideration.

Medications. Neurochemical interactions could also have impacted the study’s results. For instance, μ-opioid agonists affect DA release (Passarelli et al., 1999; Spanagel, Herz, & Shippenberg, 1990). Even a single dose of morphine has been shown to have prolonged effects on dopaminergic activity (Zhang, Zhang, Jin, Zhang, & Zhen, 2008). Most medications used to manipulate the opioid system also affect opioid receptors throughout the rest of the body (Inagaki, 2018). Moreover, even though the inclusion of a placebo is standard practice in this kind of research, the full extent of placebo effects on opioidergic activity in the present study could not be measured. Sex differences in relation to the opioid systems have been reported, with higher μ-opioid binding in women (Zubieta et al., 1999) and more severe adverse subjective effects to Naltrexone being reported by women in the luteal phase of their cycle (Roche & King, 2015). I did not record the menstrual cycle phases of female
participants and this could have had implications for the opioid-related findings, given that the majority of participants were female.

**Sample.** Considering the gender differences in both depression and opioid-related activity, a better approach for future research would be to include only one gender or to include sufficient numbers of males and females to separate out gender effects.
CHAPTER SIX:

Conclusion

The separation-distress model of depression attempts to account for the way in which depression makes people feel by seeking to identify the specific changes from ‘protest’ to ‘despair’ that lead to the psychological pain of depression. The transition from ‘protest’ to ‘despair’ is associated with very particular feeling states; a hyperactive PANIC/GRIEF system leads to feelings of distress associated with social loss, whereas a hypoactive SEEKING system leads to feelings of having lost interest in life. Depression is about affect, and yet the underlying mechanisms of the subjective experience of the psychological pain and despair of depression remain largely unexplored. The human data that is currently available is minimal and not directly focused on the affective systems of SEEKING and PANIC/GRIEF. This pioneering and complicated study sought to identify these particular feeling states in human subjects, which were previously mainly established in lower mammals. Although no definitive conclusions can be drawn from this study, the data did reveal patterns of response that are at the very least in keeping with the claim that the ‘despair’ phase of the mammalian separation distress response produces subjective affective changes in humans akin to depression, corroborating the many observations in the animal literature regarding the dopaminergic hypothesis of depression. Dampening the SEEKING system led to lack of interest, energy, motivation, emotional detachment, a desire to withdraw from the world and a significant reduction in PA. Stimulating the PANIC/GRIEF system led to a worsening of mood, a decrease in PA and feelings of social and affective disconnection. Participants with higher depression scores, that is, higher ‘despair’, experienced the stimulation of their SEEKING systems negatively, and stimulation of their PANIC/GRIEF systems diminished SEEKING to a greater extent compared to those with lower ‘despair’, suggesting that depressed affect is associated with opioid dysregulation. Similarly,
participants with higher avoidance scores, that is, higher ‘protest’, experienced a relatively smaller reduction in PANIC/GRIEF, when this system was dampened, providing some insights into the dynamics of attachment style and opioid regulation. Taken together, these results provide some ‘proof of concept’ for the conceptualization of depression as pathological ‘despair’ and that depression feels bad because a dampened SEEKING system and a stimulated PANIC/GRIEF system produce the type of feelings that are characteristic of depression. One of the strengths of this model and by extension, this study, is that it extends the scope of research on depression from a predominantly neurobiological focus to include the subjective interpretation of feelings generated by the core affective systems implicated in depression. For this reason, I contend, once again, that this conceptualization of the brain basis of depression aligns with the clinical realities of the condition more closely than most. Of equal import is that the highly variable responses of participants to the medications in this study evinces a possible reason why the efficacy of drug intervention alone in depression remains debatable, and underscores the importance of the *self*, with its individualised experiences, complexities and memories, as a crucial mediator of raw affects. The current study has contributed some observations – whilst tentative and exploratory - into the dynamics of the affectively conceptualised depressed mind by elucidating the primary process emotions upon which they are based, and the data generated from this study has added to our understanding of the subjective experience of psychoactive intervention. There is a pressing need for more data that describes succinctly these human subjective experiences. Lastly, the results of this study shed some insight into the possible limitations of current therapeutic strategies and have implications for the development of future interventions.
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# Appendix A

**Ethical Approval**

## Department of Psychology

**Report of Thesis Committee**

<table>
<thead>
<tr>
<th>Student Name:</th>
<th>ELENI PANTELIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Student #:</td>
<td>PNTLE001</td>
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<tr>
<td>Degree:</td>
<td>Ph.D.</td>
</tr>
<tr>
<td>Title (as proposed)</td>
<td>HUMAN SUBJECTIVE HOMOLOGUES OF ESTABLISHED BASIC EMOTION/NEUROPEUTIC CORRELATIONS IN LOVEK MATERIALS</td>
</tr>
<tr>
<td>Supervisor:</td>
<td>MARK SOLINS</td>
</tr>
<tr>
<td>Co-supervisor:</td>
<td></td>
</tr>
<tr>
<td>Committee members:</td>
<td>FRANK BEAUVANOT</td>
</tr>
<tr>
<td></td>
<td>LAUREN WLO</td>
</tr>
<tr>
<td></td>
<td>PMAZETTA ROONZAAAYE</td>
</tr>
</tbody>
</table>

**WE:**

1. Approve the proposal, and recommend that the student continue with the research.

2. Approve the proposal, and recommend that the student may continue with the research. However, we recommend that change(s), as noted below, be incorporated in the research, to the satisfaction of the supervisor.

3. Approve the proposal in terms of its ethical implications. If necessary, explanatory notes appear below.

4. Find the proposal unsatisfactory, for the reason(s) listed below. The student is hereby requested to re-present the proposal to a departmental thesis committee by.

**NOTES:**

1. Spell out data collection and data analysis procedures in more concrete detail.
2. Spell out more clearly in the consent form how the participants' confidentiality will and will not be protected.
3. Add in section on benefits of this study in the ethics section.

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UCP

Psychology Department
Research Ethics Committee
4th Floor, Graduate Humanities Building
University of Cape Town
Rondebosch 7701
Tel: (021) 650 3435 Fax: (021) 650 4401
e-mail: johann.leuw@uct.ac.za

8 June 2007

REC REF: solms/2007

Prof Mark Solms
Department of Psychology

Dear Professor Solms

PROJECT TITLE: Human subjective homologues of established basic emotion/neuropeptide correlations in lower mammals: A neuro-psychoanalytic study

Thank you for submitting your request to the Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study. Approval is granted for 3 years till the 30th June 2010.

Please submit an annual progress report if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approved period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC.REF in all your correspondence.

Yours Sincerely

[Signature]

Professor Johann Leuw
Chairperson, Research Ethics Committee
### Appendix B

Health Screening Questionnaire

![University of Cape Town Logo]

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**HEALTH SCREENING QUESTIONNAIRE**

### PERSONAL DETAILS

**GENERAL -**

- Name: ______________________________
- Surname: __________________________
- Date of birth: _______________________
- Gender: ____________________________
- Email address: _______________________
- Phone number: _______________________
- Cell phone: _________________________
- Weight: ____________________________ (kg)
- Height: _____________________________

### MEDICAL HISTORY

<table>
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<tr>
<th>Question</th>
<th>yes</th>
<th>no</th>
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<tbody>
<tr>
<td>Do you suffer from coronary artery disease or a circulatory or peripheral vascular disease?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>If yes, please provide details:</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you suffer from any other form of heart disease or defect?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>If yes, please provide details:</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you suffer from any metabolic or hormonal disease or condition, such as diabetes or thyroid gland disorder?</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><em>If yes, please provide details:</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you suffer from any respiratory (lung) disease or symptom(s), such as asthma or emphysema?</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>
If yes, please provide details:

| Do you suffer from any allergies, or have a history of allergic reactions to any medication? | yes | no |
| Do you suffer from any gastrointestinal disease or have a history of liver or gallbladder disease? | yes | no |
| Do you suffer from any disease or symptom(s) of the central nervous system such as epilepsy or migraine, including psychiatric disorders such as depression or panic attacks? | yes | no |
| Do you suffer from any disease or symptom(s) of the kidney or bladder, such as kidney stones or frequent urination? | yes | no |
| Do you suffer from any disease of the blood or immune system, such as anaemia or HIV/AIDS? | yes | no |
| Do you have a history of cancer? | yes | no |
| Do you suffer from any other medical condition(s), or experience any other significant symptoms? | yes | no |

MEDICATION USE

What medication, if any, are you currently using?
Appendix C

Participant Information Sheet

‘Human subjective homologues of established basic emotion correlations in lower mammals: A neuro-psychoanalytic study’

(1) You are invited to participate in a neuro-psychoanalytical study to be conducted in the Psychology Department at the University of Cape Town. Please read this information sheet carefully and do not hesitate to ask the researcher for any additional information.

(2) The purpose of this study is to explore the effects that certain psychoactive medicines have on brain emotion systems. The aims of this study are (1) to begin to systematically explore the subjective components of some basic emotion command systems that animal models have suggested may be relevant to the phenomena of separation, loss and attachment, and (2) to lay the groundwork for clinical exploitation of this knowledge for the treatment of emotional disorders.

(3) Prior to commencing participation in the study, you will be required to complete a medical screening questionnaire. The purpose of this is to ensure that you are medically fit to participate in this study.

(4) Should you agree to participate in this study, you will be required to attend six sessions in total: one ‘induction’ session and five ‘experimental’ sessions. During the ‘induction’ session, you will be asked to (a) read this Participant Information Sheet, (b) sign a consent form, (c) complete a set of psychological questionnaires, and (d) record three memorable episodes of personal loss that you have experienced. During this session, you will also be informed of the specific types of medications that you will be taking. During the ‘experimental’ session, you will be required to (a) complete a set of psychological questionnaires, and (b) undergo an analytic interview with an experienced psychoanalyst. The interviews will be audio recorded. The confidentiality of your interview and your identity will be protected. The recordings will only be viewed by an independent rater and by the researcher for the purposes of qualitative analysis. The recordings will not be viewed in any other context. Your name will not appear in any part of the dissertation or in any subsequent publications.

(5) One of four psychoactive medicines and one placebo will be administered in minimal effective dosages before each interview. All medications may cause side-effects in
some people, but the medications used in this study have been shown in previous clinical studies to be safe and well tolerated in human subjects.

(6) There are no anticipated risks involved in this research, but if you should experience any form of physical or psychological distress, please inform the researcher immediately. Also, should you feel that you need to consult a doctor, you will be referred for medical treatment, and the costs will be covered by the administrators of this study.

(7) This study forms part of a Ph.D. degree at the University of Cape Town (UCT).

(8) The study has been reviewed by the UCT Psychology Department’s ethics committee.

(9) If you decide to take part, this information sheet will be given to you to keep and you will be asked to sign a consent form.

(11) You can withdraw from the study at any time, without having to provide a reason and all costs reimbursed.

(12) If you have any questions regarding this study, or concerns regarding the manner in which the study was conducted, please contact Eleni Pantelis on (021) 650 3437 or 082 775 2081.
Appendix D

Consent form

Participant:
I, (name of participant) ____________________________________________________________
of (address) _________________________________________________________________
agree to participate in the research study entitled:

‘Human subjective homologues of established basic emotion correlations in lower mammals: A neuro-psychoanalytic study’

I fully understand the aims of this study, which has been thoroughly explained to me.
I understand that I will ingest either a psychoactive medicine and/or placebo.
I fully understand and accept that I will be expected to divulge personal information regarding my thoughts and feelings. I do so on the understanding that all identifying information revealing the link between me and my data will be erased.
I understand that my consent is entirely voluntary and that I may withdraw from the research study at any time and for any reason.

Print Name:________________________ Signature: ____________________________
Date: | | | | | | | | | | | | | | | | | | | | Time: | | | | (24 hours)