Hippocampal Activation and Memory Encoding in Borderline Personality Disorder

by

Dean Carcone

A thesis submitted in conformity with the requirements for the degree of Master of Arts, Clinical and Counseling Psychology, Field: Clinical Psychology

Graduate Department of Psychological Clinical Science

University of Toronto

© Copyright by Dean Carcone 2016
Hippocampal Activation and Memory Encoding in Borderline Personality Disorder

Dean Carcone

Master of Arts, Clinical and Counselling Psychology, Field: Clinical Psychology
Graduate Department of Psychological Clinical Science
University of Toronto
2016

Abstract

Individuals with borderline personality disorder (BPD) report everyday problems with forgetfulness and display deficits on standardized measures of memory functioning. The medial temporal lobe, involved in memory encoding and consolidation, is smaller in individuals with BPD and shows an altered pattern of resting metabolism. The neural correlates of disrupted memory formation in BPD have not been studied outside of the context of emotionally-valenced material. To examine the neural underpinnings of memory encoding in BPD, the present study assessed eight females with BPD and an equal number of age- and sex-matched non-psychiatric controls. Participants viewed visual scenes during functional magnetic resonance imaging scanning and subsequently completed a recognition memory test outside the scanner. Compared to controls, individuals with BPD exhibited less activation in the right hippocampus for subsequently remembered versus forgotten scenes. These results suggest that hippocampal dysfunction during the formation of memories may underlie the memory disturbances associated with BPD.
Acknowledgements

I would like to express my sincere gratitude to Dr. Anthony Ruocco and Dr. Andy Lee, my co-supervisors for this master’s thesis, for their inspiration, encouragement, and unwavering support at all stages of this project. I am so fortunate to have had the benefit of working with these two phenomenal researchers and learning from their combined expertise. I would also like to thank Dr. Amanda Ulaszek for her participation on my master’s thesis committee, her incisive suggestions in the development of this project, and her emphasis on considering what data mean to the “real world”.

This project would not have been possible without the support and hard work of the members of the Clinical Neurosciences Laboratory and the Lee Lab. Specifically, I would like to thank Bryanna Graves and Jie Chang for the work that they have done behind the scenes to keep the lab running like clockwork. I would also especially like to thank Jacob Lang for his dedication and time during piloting of this study and scanning participants.

I must also thank my wonderful parents for their incredible and selfless emotional and nutritional support over the last two years. Thank you to Holly Howe for her camaraderie and indirect motivation to keep working hard. Thanks also to Sarah Wright for ensuring that I didn’t miss out on all aspects of life. Finally, I would like to thank the other members of my graduate cohort, Matthew Quitasol, Phillip Desormeau, Kyrsten Grimes, and Lê-Anh Dinh-Williams; I could never have asked for more supportive group of friends at my side during this process.
# Table of Contents

Chapter 1. Introduction ...........................................................................................................1

1.1 Brain Regions Associated with Memory .........................................................................2

1.2 Functional Neuroimaging Studies of Memory in BPD ..................................................4

1.3 Neuroimaging Paradigms Examining Memory Encoding .............................................7

1.4 Aims of the Present Study ............................................................................................9

Chapter 2. Method ................................................................................................................11

2.1 Participants .....................................................................................................................11

   2.1.1 Patients with BPD ..................................................................................................11

   2.1.2 Non-Psychiatric Controls .....................................................................................12

   2.1.3 Neuroimaging Exclusion Criteria .........................................................................12

2.2 Procedures .....................................................................................................................12

   2.2.1 General Experimental Procedures ......................................................................12

   2.2.2 Behavioural Procedure .......................................................................................15

2.3 Behavioural Data Analysis ...........................................................................................17

2.4 Imaging ........................................................................................................................17

   2.4.1 Data acquisition ..................................................................................................17

   2.4.2 Image Pre-processing ........................................................................................18

   2.4.3 Statistical Analysis ..............................................................................................18

Chapter 3. Results ................................................................................................................20

3.1 Participant Characteristics and Behavioural Findings ...............................................20

3.2 Self-Report Findings .....................................................................................................20

3.3 Neuroimaging Findings ...............................................................................................21
3.3.1 Subsequent memory effect .................................................................................. 21
3.3.2 Subsequent memory between groups ................................................................. 21
3.3.3 Relationship between hippocampal activation and symptom measures .......... 22

Chapter 4. Discussion ................................................................................................... 23
Tables................................................................................................................................. 31
Figures............................................................................................................................... 34
References......................................................................................................................... 37
List of Tables

**Table 1.** Summary of diagnostic comorbidities within the final patient group ..........................31

**Table 2.** Summary of group characteristic and task performance ..............................................32

**Table 3.** Summary of group responses to self-report measures ....................................................32

**Table 4.** Peak activation of clusters associated with remembered and forgotten scenes. ........33
List of Figures

*Figure 1.* Behavioural Paradigm ........................................................................................................34

*Figure 2.* Regions of brain activation associated with subsequent memory and subsequent forgetting across groups ........................................................................................................35

*Figure 3.* Hippocampal deactivation in patients compared to controls for remembered > forgotten scenes .......................................................................................................................36

*Figure 4.* Mean hippocampal % signal change within 5mm of the peak comparison voxel .....36
Borderline personality disorder (BPD) is a mental disorder with a lifetime prevalence of approximately 1-2% in the general population (Lenzenweger, Lane, Loranger, & Kessler, 2007). The disorder is characterized by interpersonal and affective instability, impulsive and suicidal behaviours, and an unstable sense of self (American Psychiatric Association, 2013). Disturbances in cognition are also frequently identified in BPD (Mauchnik & Schmahl, 2010; Ruocco, 2005), and memory processes, in particular, may be affected. Subjective reports from individuals with BPD indicate that forgetfulness may be a common complaint in their day-to-day lives (Ruocco, Lam, & McMain, 2014). Compared to adults without a history of mental disorder, individuals with BPD report significantly more subjective memory complaints (Beblo et al., 2014), and the severity of BPD symptoms appears to be related to the degree of memory impairment reported by patients (Beblo et al., 2014; Park et al., 2012).

Accompanying subjective reports of memory disturbances, patients with BPD also display objective cognitive deficits on a range of neuropsychological measures. Although individual studies vary in the nature and extent of these deficits (Cornelius et al., 1989; Dinn et al., 2004; Sprock, Rader, Kendall, & Yoder, 2000), meta-analytic work suggests that patients with BPD show deficits in several cognitive domains (Ruocco, 2005). Compared to non-psychiatric controls, patients with BPD perform significantly poorer on standardized tests of attention, learning and memory, processing speed, visuospatial abilities, and executive functions (i.e., cognitive flexibility and planning), with effect size differences (Cohen’s $d$) ranging from 0.29 to 1.43. In particular, a medium size effect ($d = 0.66$) was observed for the learning and episodic memory domain, which collapsed non-cued recall performance from tests such as the
Wechsler Memory Scales (Wechsler, 1945) and Rey-Osterrieth Complex Figure Test (Rey, 1944). When verbal and visual memory tests were considered separately, however, the effect sizes ($d = 0.45$ and $d = 1.59$, respectively) highlighted potentially meaningful material-specific deficits in episodic memory for patients with BPD (Ruocco, 2005). These findings suggest that patients with BPD display deficits in episodic memory, perhaps with a greater decrement to visual than verbal memory, although the neural mechanisms underlying these disturbances in memory formation has yet to be established in BPD.

1.1 Brain Regions Associated with Memory

The medial-temporal lobe (MTL) is the region of the brain suggested to be primarily responsible for the formation of declarative memories (Squire, Stark, & Clark, 2004; Squire & Zola-Morgan, 1991). Although memories are thought to be ultimately stored in the neocortex (Wiltgen, Brown, Talton, & Silva, 2004), human and animal lesion studies, as well as histological studies, have demonstrated the different roles that the MTL and its subregions play in memory consolidation. Key regions of the MTL include the hippocampus as well as the entorhinal cortex (EC), perirhinal cortex (PRC), and parahippocampal cortex (PHC). The majority of hippocampal input comes from the EC, which receives connections from the rest of the brain either directly or through the adjacent PRC and PHC (Squire & Zola-Morgan, 1991). Additional roles of the MTL beyond declarative memory have also been suggested, including higher-order perception (Lee, Yeung, & Barense, 2012; Murray, Bussey, & Saksida, 2007), spatial cognition (Mullally & Maguire, 2013; Nadel & MacDonald, 1980; O'Keefe, 1990), and working memory (Ranganath & Blumenfeld, 2005). Although delineating discrete responsibilities of MTL subregions has been met with contradictions and inconsistent results (Squire & Wixted, 2011), some degree of functional division-of-labour likely exists between
these areas (Davachi, 2006; Montaldi & Mayes, 2011; Murray et al., 2007; Wolk, Dunfee, Dickerson, Aizenstein, & DeKosky, 2011). Reductions of the grey matter of this region have also been linked to cumulative stress and a number of psychological disorders (Fornito, Yücel, Patti, Wood, & Pantelis, 2009; Frodl & O'Keane, 2013; Kühn & Gallinat, 2013).

Individuals with BPD exhibit structural differences in regions of the MTL when compared to adults without a history of mental disorder. Voxel-based morphometry studies suggest that women with BPD have lower grey matter in the hippocampus and PHC bilaterally, irrespective of comorbid depression or history of childhood sexual abuse (Soloff, Nutche, Goradia, & Diwadkar, 2008). There may be a lateralized pattern to MTL volumetric findings in BPD as some studies have only found significant differences in the left or subregions within the right hippocampus (O'Neill et al., 2013; Rossi et al., 2015). The magnitude of these reductions appears to be related to the clinical severity of BPD symptoms, including impulsivity (Soloff et al., 2008) and suicidality (Soloff et al., 2012). Additionally, one study showed that only patients fulfilling more than the minimum number of criteria for BPD or with a lifetime history of posttraumatic stress disorder (PTSD) had reduction in hippocampal volume. (Kreisel et al., 2015). A meta-analysis, however, has shown that hippocampal volumes are significantly smaller bilaterally in BPD than non-psychiatric controls, by an average of 11% (Ruocco, Amirthavasagam, & Zakzanis, 2012). Additionally, it was shown that these differences are not more pronounced in samples with higher proportions of co-morbid mental disorders or untreated patients. These structural differences are accompanied by findings of lower resting metabolic activity in the left hippocampus in individuals with BPD as compared to non-psychiatric controls (Juengling et al., 2003).
1.2 Functional Neuroimaging Studies of Memory in BPD

Only a small number of studies have used functional magnetic resonance imaging (fMRI) to examine brain functioning associated with episodic memory in BPD. Of these studies, nearly all incorporated materials that were exclusively emotionally valenced (i.e., the stimuli were intended to elicit an emotional response). Additionally, some were described as studies of autobiographical memory, a distinct form of episodic memory that is associated with identity and self-perception (Conway & Pleydell-Pearce, 2000). Driessen et al. (2004) examined differences in cued autobiographical memory recall in a sample of 12 patients with BPD and compared those with and without comorbid PTSD. A blocked design was used to contrast brain activity associated with recall of traumatic versus non-traumatic events, which was then compared between groups. BPD patients without PTSD group showed predominant activity in regions of the prefrontal cortex (PFC) during recall of trauma, while more sensorimotor and temporolimbic activity was found in patients with PTSD. Given that the primary contrast of interest in this study was between emotional conditions, it may be argued that this study examined emotional rather than autobiographical memory processing.

Schnell et al., (2007) also purported to investigate autobiographical memory retrieval in patients with BPD, using fMRI to compare patterns of neural activation in this group with non-psychiatric controls. In an event-related design, participants were presented with emotional images from the Thematic Appreciation Test (TAT) or neutral images from the International Affective Picture System (IAPS) as autobiographical memory cues. Compared to neutral images, emotional images elicited increased Blood Oxygen Level Dependent (BOLD) responses in patients for a variety of regions, including the bilateral orbitofrontal and insular cortex, left PHC, anterior cingulate and medial PFC for BPD patients. Where controls exhibited differential
Amygdala activation based on stimulus category, this variation was not observed for BPD patients. Similar to Driessen et al. (2004), this contrast (emotional > neutral) is expected to reveal differences primarily in emotional processing rather than autobiographical memory recall. The study also reported regions of increased activation between patients and controls following neutral memory cues. Greater activation in the left subcallosal gyrus and right orbitofrontal, anterior cingulate, and superior temporal gyrus was observed for patients compared to controls.

Aside from research on autobiographical memory in BPD, a single fMRI study purported to measure non-autobiographical memory retrieval processes. Mensebach et al. (2009) compared blocks of verbal recall and lexical retrieval to examine episodic and semantic memory retrieval, respectively, in a sample of BPD patients and non-psychiatric controls. No significant differences were found between patients and controls on neuropsychological tests of verbal episodic or semantic memory retrieval on the day prior to scanning. However, patients showed large task-specific increases in activation in specific brain regions during semantic and episodic memory recall. While performing a verbal fluency task, which was used to examine semantic memory retrieval processes, activation was increased in the posterior and left anterior cingulate cortex, right fusiform gyrus, and left postcentral gyrus in patients compared to controls. Episodic memory retrieval, examined during free recall of a word list, produced increased activity in the bilateral posterior cingulate cortex, left middle and superior temporal gyrus, and the right angular gyrus in patients compared to controls. These increases in activation may suggest that greater neural recruitment is necessary to reach control-level performance (Mensebach et al., 2009), potentially reflecting reduced neural efficiency in memory retrieval.

Although the functional neuroimaging studies described above have focused exclusively on processes related to memory recall, one additional fMRI study has employed a paradigm that
may highlight memory encoding processed in BPD. While viewing emotionally negative and neutral images from the International Affective Pictures System for the purpose of immediate recognition, BPD patients exhibited diminished activation compared to controls in areas including the hippocampus, the anterior cingulate cortex (ACC), the superior parietal cortex (SPC), precuneus, and the dorsolateral prefrontal cortex (dLPFC; Soloff, White, Omari, Ramaseshan, & Diwadkar, 2015). In this mixed block/event-related design, patterns of deactivation were similar between negatively valenced and neutral images, as compared to positive, during what the authors term “episodic memory encoding”. Distinct patterns, however, were associated with neutral and negative emotional valence during episodic memory retrieval. A contrast between recall of negative and positive images revealed lower activation in the ACC, dLPFC, and hippocampus for patients compared to controls, where only deactivation in the basal ganglia was observed for neutral versus positive images. Although episodic memory encoding must be occurring in order for patients to perform episodic memory retrieval, the contrasts employed in this simple paradigm were constructed to highlight differences in the memory encoding process as it relates to emotional valence, rather than the underlying memory encoding process itself. Whether or not a picture was subsequently recognized was not considered in the analysis of brain activation patterns.

Although none of the studies described above employed similar designs, many reported overlapping patterns of increased activation of prefrontal and cingulate cortex associated with memory retrieval processes in BPD (Driessen et al., 2004; Schnell et al., 2007). With respect to the MTL, increased activation in the PHC was observed during emotional autobiographical memory retrieval (Schnell et al., 2007), while lower activation in the hippocampus was observed for emotional memory encoding (Soloff et al., 2015). In addition, other regions associated with
hyperactivity during autobiographical memory retrieval were found to be underactive during encoding of negatively valenced emotional pictures, including dorsolateral prefrontal and anterior cingulate cortices. However, these regions were also found to be underactive during subsequent retrieval of these emotional pictures, highlighting a potential inconsistency in either these results or the distinct processes related to autobiographical memory processing. In summary, three of these four studies focused on memory retrieval processes and one on both memory retrieval and encoding processes. All but one of these studies (Mensebach et al., 2009) used emotionally valenced stimuli and employed contrasts which would highlight regions associated with emotional rather than mnemonic processing. It can be argued that the fundamental neural underpinnings of memory encoding, an important facet of episodic memory, have still has not been examined in BPD. A number of paradigms have been developed to allow direct examination of episodic memory encoding which may be useful in studying this patient population.

1.3 Neuroimaging Paradigms Examining Memory Encoding

Early research investigating the neural correlates of memory encoding employed PET and electroencephalography (EEG). This research often employed what has been coined a “novelty detection paradigm” (Tulving, Kapur, et al., 1994; Tulving, Markowitsch, Kapur, Habib, & Houle, 1994), which involves presenting novel and familiar visual stimuli to a participant and later comparing how neural activations compare between these two conditions. According to the “novelty/encoding hypothesis” (Tulving, Markowitsch, Craik, Habib, & Houle, 1996), increases in brain activity accompanying unfamiliar stimuli represent both novelty detection and encoding of that stimulus into memory. However, the precise contributions of novelty detection versus memory encoding cannot be delineated using this paradigm. An
alternative approach has been to consider brain activity specifically related to successfully encoded versus forgotten items: the difference-due-to-memory (“Dm”) effect (Paller, Kutas, & Mayes, 1987). Using EEG, evoked potentials can be recorded for visual stimuli and then grouped based on whether or not a participant remembers seeing that stimulus (Sanquist, Rohrbaugh, Syndulko, & Lindsley, 1980). Distinct waveforms, including a pronounced late positive component, are observed based on recognition memory performance (Sanquist et al., 1980), as well as depth of encoding (Paller et al., 1987). The Dm effect has been used across many neuroimaging modalities, revealing essential information about the networks involved in successful memory encoding.

Event-related fMRI experiments have also explored the Dm effect using the “subsequent memory” paradigm. By presenting words (Wagner, 1998) or images (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998) to participants undergoing fMRI, and then comparing BOLD responses for stimuli which were subsequently remembered versus forgotten, regions of the PFC and MTL are found to predict successful stimulus encoding. Furthermore, this activity is related only to actual encoding success, rather than subjective judgements of success at the time of encoding (Kao, Davis, & Gabrieli, 2005). Meta-analysis has revealed reliable hippocampal activation associated with memory encoding (Spaniol et al., 2009), often observed bilaterally (Kim, 2011). There is debate as to whether there exists functional specialization of the hippocampus along the longitudinal axis with respect to episodic memory encoding (Fernández et al., 1998; Greicius et al., 2003). However, these studies have been based on blocked rather than event-related designs and therefore did not employ the traditional subsequent recall paradigm. Although the distribution of hippocampal recruitment may be unclear, PHC activation has also been found to predict subsequent memory (Strange, Otten, Josephs, Rugg, & Dolan,
The laterality of this MTL activity, however, may be related to the nature of the stimuli being encoded (i.e., verbal versus non-verbal materials; Kelley et al., 1998). Differences observed in activation using a subsequent memory paradigm may be partially explained based on whether participants were encoding verbal or non-verbal stimuli. A meta-analysis of 74 subsequent memory fMRI studies has highlighted differences in the pattern of activation expected when employing verbal versus non-verbal memoranda (Kim, 2011). In general, subsequent memory tends to be related to activity in five regions: the fusiform cortex, MTL, PMC, posterior parietal cortex (all bilaterally), and the left inferior frontal gyrus. The left inferior frontal gyrus is more active during verbal rather than picture encoding (also discussed in Wagner et al., 1998), with the converse true for the fusiform cortices. While verbal encoding recruits only the left MTL, picture encoding recruits the MTL bilaterally, with stronger activation observed for both sides during picture compared to word encoding (Kim, 2011).

1.4 Aims of the Present Study

The purpose of the present study is to investigate hippocampal activation patterns associated with successful memory encoding in BPD. Brain activity related to successful memory encoding will be compared between individuals with BPD and non-psychiatric controls. Groups will be matched on age and memory recognition scores to account for potential confounds related to brain morphology and task performance on brain activation. Differences found between these groups may help identify the pathophysiology underlying memory disturbances in BPD, which could illuminate biological targets for cognitive interventions. In order to engender the most robust activation related to subsequent memory, visual stimuli will be presented for encoding. Although similar paradigms have been used in other clinical populations
(Hamilton & Gotlib, 2008; Hayes et al., 2011), this will be the first functional neuroimaging study to use a subsequent memory paradigm to examine memory encoding in BPD. It will also be the first to investigate the underpinnings of fundamental memory processes in this patient group, independent of emotionally-valenced stimuli.

Given the previous research highlighting differences in hippocampal activation during memory-related processes in BPD, it is predicted that patients with BPD will demonstrate a different pattern of hippocampal activity compared to non-psychiatric controls related to successful memory encoding. How these patterns may differ is open to speculation. It is possible that activity underlying successful encoding will be reduced compared to controls, an effect observed in PTSD when encoding traumatic pictures (Hayes et al., 2011; Soloff et al., 2015), possibly reflecting deficits in the underlying encoding process. Alternatively, stronger or more widespread activation of regions related to memory encoding may be observed for patients compared to controls (similar to Mensebach et al., 2009), suggesting that additional neural recruitment is necessary to compensate for inefficient memory processes. The results of this study should help clarify the nature of memory deficits in BPD by isolating dysfunctions in neural systems that relate to disrupted encoding of new memories.
2.1 Participants

2.1.1 Patients with BPD. Ten right-handed female patients with BPD were recruited from the research registry of the Clinical Neurosciences Laboratory (CNL) at the University of Toronto Scarborough. All patients met diagnostic criteria for BPD based on the Structured Interview for DSM-IV Personality (SIDP-IV; Pfohl, Blum, & Zimmerman, 1997). Recruitment was limited to patients ages 18 to 55 years, without a current or lifetime diagnosis of any DSM-IV psychotic disorder, bipolar I disorder, or current alcohol or substance use disorder, as assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition (SCID-I/P; First, Spitzer, Gibbon, & Williams, 2012). Patients were also excluded if they had any developmental disorder (e.g., autism-spectrum disorder, Down’s syndrome), neurological illness (e.g., multiple sclerosis, epilepsy, stroke), serious physical illness (myocardial infarction, hypothyroidism), significant hearing or vision impairment, or had sustained any head trauma resulting in loss of consciousness for longer than 20 minutes.

One patient was excluded from analysis due to a scanner malfunction. One other patient was excluded from participation following a positive urine drug screen. Eight patients (mean age = 28.5 years, SD = 8.4 years) were included in the final sample. Five of the eight patients were on psychoactive medication, including antidepressants (n = 5), anticonvulsants (n = 4), antipsychotics (n = 3), anxiolytics (n = 2), sedatives (n = 1), stimulants (n = 1), dissociative anesthetics (n = 1), and sympatholytic (n = 1). Three patients were prescribed three or fewer medications at the time of participation, and the remaining two were currently prescribed eight or more medications. All patients met criteria for multiple additional current or past psychiatric
diagnosis at the time of their participation. A summary of these additional diagnoses is included in Table 1.

2.1.3 Non-Psychiatric Controls. Fifteen right-handed female controls were recruited from the CNL research registry. Individuals were excluded if they had any personal history of mental disorder, as assessed using the SCID-I/P and SIDP-IV. Additionally, controls did not have substantial Cluster A or Cluster B personality disorder traits (e.g., four or more traits from these clusters). Controls were also excluded if they had any developmental disorder, neurological illness, serious physical illness, significant hearing or vision impairment, or had sustained any head trauma resulting in loss of consciousness/confusion for longer than 20 minutes. Two healthy controls were excluded from analysis due to scanner malfunction. Of the remaining 13 controls, a sample of 8 participants was selected to provide a comparison group matched to the patient group on both age (mean age = 27.6 years, SD = 8.3 years) and behavioural performance on the task.

2.1.3 Neuroimaging Exclusion Criteria. Patients and controls were also required to not meet any exclusion criteria for safe MRI scanning. These criteria were evaluated twice, once during screening and once immediately prior to scanning by a Magnetic Resonance (MR) technician. Exclusion criteria included pregnancy, severe claustrophobia, and any metal in the body (including medical implants, pacemakers, cochlear implants, and aneurysm clips), considering all of the criteria outlined by fMRI scanning policy at the Center for Addiction and Mental Health (CAMH) Research Imaging Centre.

2.2 Procedures

2.2.1 General Experimental Procedure. The protocol for this study was approved by the CAMH and University of Toronto Research Ethics Boards. Following a brief screening
telephone interview to ensure that eligibility criteria were met, participants were scheduled to
attend approximately three hours of experimental procedures at the College Street site of CAMH.
After providing written informed consent on the day of the study, all participants provided a
urine sample on which a urine toxicology screen and pregnancy test were performed. One patient
returned a positive result for the toxicology screen and was no longer eligible to continue
participation. Healthy controls completed the same semi-structured clinical interviews as
patients, administered by graduate-level psychology students supervised by a licensed
psychologist or by a licensed psychologist.

All participants also completed self-report questionnaires as part of the study. The first
measure was a self-report version of the Zanarini Rating Scale for Borderline Personality
Disorder (ZAN-BPD; Zanarini, 2003), a nine-item questionnaire uses to estimate the severity of
BPD symptomology. The measure produces a score (0 to 36) representing the severity of the 9
DSM-IV symptom criteria for BPD, each assessed on a 5-point anchored rating scale. The total
score can be divided into four symptom subscales: affect, cognition, impulsivity, and
interpersonal. The measure has exhibited high construct (convergent and discriminant) validity,
reliability (Cronbach’s alpha = .85), and high sensitivity to changes in BPD symptom severity
(Zanarini, 2003),

Participants also completed the Memory Functioning Questionnaire (MFQ; Gilewski,
Zelinski, & Schaie, 1990), providing dimensional assessments of a participant’s perceived
everyday memory functioning. This measure included 64 questions answered by selecting a
number from 1 to 7 indicating either frequency or severity of a given memory difficulty, with
lower numbers indicating higher frequency or stronger severity. Total scores range from 64 to
448, with scores below 200 taken to indicate moderate perceived memory disturbance, and
scores below 100 indicating substantial awareness of memory difficulties. The questionnaire has exhibited good-to-excellent internal consistency (Cronbach's alpha > .83; Gilewski et al., 1990) and moderate concurrent validity with independent measures of memory performance (Zelinski, Gilewski, & Anthony-Bergstone, 1990).

Additionally, participants completed the Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983) to assess current subjective stress levels. This measure is comprised of ten questions related to emotional experience during the previous month and has demonstrated high construct validity and internal consistency (Cronbach's alpha = .89; Roberti, Harrington, & Storch, 2006). Participants indicate on a 0-to-4 point scales how often a given experience has occurred during the previous month, with total scores ranging from 0 to 40. Four items are coded in reverse directions and are inverted when calculating total scores.

Finally, participants completed the online version of the Dimensional Assessment of Personality Pathology – Basic Questionnaire (DAPP-BQ; Livesley & Jackson, 2009), a comprehensive personality inventory assessing the severity of 18 dimensions of personality psychopathology. This extensive self-report questionnaire, comprising 290 items rated on a 5-point scale of agreement, is based on Livesley’s proposed 18-factor model of personality pathology (Livesley, Jackson, & Schroeder, 1992). Clusters of dimensional scores along certain scales are taken to represent higher-order domains, including emotional dysregulation, dissocial behaviour, social avoidance, and compulsiveness. Scales within this measure have demonstrated high convergent validity with related measures (r’s > .56) and high internal (Cronbach's alpha > .84) and test-retest reliability (interclass correlations > .84; (Livesley & Jackson, 2009).

Prior to undergoing MRI scanning, participants were allowed to complete a set of practice trials for the fMRI task until they felt comfortable with the timing of the task and their
response options. Participants also completed a short consultation with an MR technologist to ensure their safety before entering the MRI scanner. The neuroimaging component of the experiment lasted approximately 45 minutes and is explained in greater detail below. During scanning, participants were presented with images of scenes and were requested to make a button press in response to each scene. Immediately following completion of the scan, participants completed an unexpected recognition memory test on a laptop computer for the images which were presented to them in the scanner. Participants received monetary compensation for their participation and a picture of their brain if requested.

2.2.2 Behavioural Procedure. Participants were asked to make a button-press response to 225 images presented to them while undergoing fMRI scanning. All stimuli were delivered using E-Prime (Version 2.0; Psychology Software Tools), with responses collected using the same software. Images were presented on either the left or right side of the screen projected onto a mirror placed in front a participant, with a pixel resolution of 1280x768. Two-thirds of the images were greyscale pictures of scenes, with a resolution of 350x350 pixels. Half of the scenes depicted indoor environments and the remaining half depicted outdoor environments. Images remained on the screen for 3000ms, followed by the text “Response?” for 1000ms. Once the image was replaced by the text, a participant was asked to indicate if the prior scene was indoor or outdoor by pressing one of two buttons on a button box placed in their right hand. Presentation of indoor and outdoor scenes was counterbalanced across left and right sides. The intended purpose of this lateralized scene presentation was to allow division of subsequently remembered scenes into those recognized with additional source memory versus those without (i.e. episodically remembered versus familiar scenes). In order to provide a baseline condition matched for visual stimulation, the remaining third of the images depicted scrambled greyscale
scenes of the same resolution, with a 7x7 tile scramble tessellation. See Figure 1 for a sample of
the visual stimuli used for the fMRI experiment. Half of these scrambled scenes contained a
small (25 pixel diameter) dark grey circle located somewhere in the image. Following the
presentation of a scrambled image, a participant’s task was to identify if the circle was present or
absent in the image by pressing one of the same two buttons on the button box. Trials were
separated by an inter-stimulus interval jittered approximately along a chi-squared distribution
with a mean of 4500ms (Hagberg, Zito, Patria, & Sanes, 2001). Additional time was included at
the beginning and end of each experimental run to provide baseline data for subsequent general
linear models. The responses made by the participant were unrelated to the following subsequent
memory task and were included to ensure that a participant was looking at and paying attention
to the images presented. Trials were divided into three 12-minute blocks of 75 images, with the
order of block presentation counterbalanced within and between groups.

Immediately following completion of the third of three blocks of image presentation,
participants completed a subsequent recognition memory test outside the scanner for the
previously presented unscrambled scenes. Participants were shown 225 greyscale images of
scenes on the center of a laptop screen. All of the 150 scenes presented during MRI scanning
were shown, as well as 75 images of scenes not previously seen by the participant. Images were
presented individually, with the order of image presentation randomized for each participant.
While an image remained on the screen, participants made self-paced keyboard button-press
responses to one, two, or four questions. Initially, participants were asked, “Have you seen this
picture before?” (Yes/No). If yes, a participant was then asked, “Can you remember what side of
the screen this picture was shown on?” (Yes/No). If yes, a participant was then asked “Where
was this picture on the screen? (Left side/Right side), followed by, “How confident are you of
your answer?” (Not/Somewhat/Very confident). Only responses to the first question were used in subsequent analyses, as low accuracy on side recall (mean accuracy = 13.1%, SD = 10.9%) resulted in insufficient statistical power for examining the neural correlates of source memory.

2.3 Behavioural Data Analysis

Overall performance on the subsequent memory test was indexed by calculating a d-prime score for each participant. Based on responses to the subsequent memory test, a trial fell into one of four categories: remembered (correctly recognized as old), forgotten (incorrectly identified as new), correct rejection (correctly identified as new), and false alarm (incorrectly identified as old). D-prime was calculated for each participant by subtracting the z-score for false-alarm-rate (false-alarms/total new scenes) from the z-score for hit-rate (remembered/total old scenes). One patient did not incorrectly identify any foil as new, preventing calculation of a z-score for false-alarm-rate. A value of 0.1 was substituted for 0, and the calculation was repeated.

2.4 Imaging

2.4.1 Data acquisition. Neuroimaging data were collected at the Research Imaging Centre of CAMH, using a 3T Signa MR System (GE Medical Systems, Milwaukee, Wisconsin). Functional imaging employed a Blood Oxygen Level Dependent (BOLD) Spiral In/Out sequence (Glover, 2012; 47 slices, 0 mm inter-slice distance, 3.5mm³ voxel size, 3000ms repetition time, 30ms echo time, 60° flip angle, 64x64 matrix size, 225 volumes per experimental block). High-resolution 3D anatomical scans were also obtained using a T1 BRAVO sequence (200 slices, 0.9mm³ voxel size, 6.7ms repetition time, 3ms echo time, 8° flip angle, 256x256 matrix size) to allow registration of functional images onto a standard template.
2.4.2 Image pre-processing. All neuroimaging data were preprocessed and analyzed using the fMRI Expert Analysis Tool (FEAT) version 6.00 and other software included in the FMRIB Software Library (FSL Version 5.0.8; http://www.fmrib.ox.ac.uk/fsl). Initially, visual inspection was performed on the raw functional data to identify gross movement, distortions, or missing data. Following the deletion of the first three volumes of each run due to signal instability, motion correction was performed on individual runs using the Motion Correction FMRIB’s Linear Regression Tool (MCFLIRT; Jenkinson, Bannister, Brady, & Smith, 2002). Preprocessing stages also included grand mean scaling, high-pass temporal filtering with a cut-off of 90 seconds, and spatial smoothing with a 6mm Full-Width Half-Maximum Gaussian kernel. Functional brain images were extracted using the Brain Extraction Tool (BET; Smith, 2002) and coregistered to individual anatomical space using boundary-based registration performed using FMRIB’s Linear Image Registration Tools (FLIRT; Andersson, Jenkinson, & Smith, 2007). Subsequently, the data were normalized to the Montreal Neurological Institute 152 (MNI-152) 2mm standard brain template using the FSL Nonlinear Registration Tool (FNIRT; Jenkinson et al., 2002) allowing for 12 degrees of freedom.

2.4.3 Statistical analysis. Once preprocessed, each run of the experiment from each participant was submitted to a general linear model (GLM). Three event types were specified as explanatory variables: scrambled images, images subsequently remembered, and images subsequently forgotten. Given that these events were identified based on later performance on a recognition memory test, a different number of events was provided for each run and each participant. These events were convolved with a standard double-gamma model of the hemodynamic response function (HRF), leading to one parameter estimate for each explanatory variable for each run. Individual contrasts between subsequently remembered and subsequently
forgotten images within each run were also generated in both directions (i.e. ‘remembered >
forgotten’ and ‘forgotten > remembered’). Individual runs were then combined at the individual
subject level using fixed-effects analysis.

Two higher-level group analyses were then performed on the ‘remembered > forgotten’
and ‘forgotten < remembered’ contrasts. The first analysis implemented a GLM combining data
across all patients and controls using FMRIB’s Local Analysis of Mixed Effects (FLAME)
stages 1 and 2. Significant regions of activity at the whole-brain level were determined using
cluster-wise inference at $p < 0.05$ family-wise error (FWE) corrected with a cluster-forming
threshold of $z = 2.3$. Significant regions of activation were subsequently identified using the

The second group-level analysis employed a GLM to contrast the patient and control
groups for the ‘remembered > forgotten’ and ‘forgotten > remembered’ contrasts using a mixed-
effects (FLAME 1+2) analysis. Due to our a priori hypotheses, the bilateral hippocampus was
examined as a region-of-interest (ROI) using an anatomical mask containing voxels with a
greater than 50% likelihood of capturing the hippocampus, according to the Oxford-Harvard
Subcortical Atlas. Significant regions of activity within the hippocampus were determined using
cluster-wise inference at $p < 0.05$ FWE-corrected for a small volume (SVC) with a cluster-
forming threshold of $z = 2.3$. The peak hippocampal voxel differentiating patients and controls
for the remembered-forgotten contrast was located. A mask representing a 5mm sphere centered
on this peak voxel was used to query the mean % signal change of that region for the
‘remembered > forgotten’ contrast within each participant.
Chapter 3

Results

3.1 Participant Characteristics and Behavioural Findings

Participants performed well on the recognition memory test, with an average d-prime of 1.01 (SD = 0.57) for the correct identification of a previously presented scene. Across groups, an average of 68.75 (SD = 26.94) scenes were recognized correctly as old and 81.25 (SD = 26.94) scenes forgotten. See Table 2 for performance separated by group. This proportion of remembered versus forgotten scenes is ideal for neuroimaging analyses, allowing a similar number of trials to be considered for each condition. Given that members of the control group were selected to be matched with BPD patients on age and performance, no significant difference was found between the groups in age, $t(14) = 0.21, p = .84$, scenes correctly recognized, $t(14) = 0.92, p = .37$, or d-prime, $t(14) = 0.94, p = .36$. Additionally, there was no significant difference between groups in reaction time to recognition memory prompts during the subsequent memory test, $t(14) = 1.07, p = .30$. Furthermore, there was no significant difference in accuracy, $t(7) = 1.62, p = .15$, of responses collected during the MRI scan ($M = 83.55\%$ correct, SD = 38.65).

3.2 Self-Report Findings.

BPD patients scored significantly higher than controls on the ZAN-BPD, $t(8) = 6.16, p < .001$. See Table 3 for mean scores broken down by group. Patients also perceived themselves to be under significantly more stress during the past month than controls, scoring significantly higher on the PSS, $t(14) = 6.33, p < .001$. Additionally, patients reported significantly more day-to-day memory complaints on the MFQ than controls, $t(11) = 3.47, p < .005$. 
The DAPP-BQ was highly sensitive to the personality pathology present in this patient sample. Patients exhibited significantly elevated scores compared to controls on most scales of the DAPP-BQ. The four scales demonstrating the largest difference between groups map closely onto BPD symptom dimensions: Affective Lability, \( t(14) = 12.64, p < .001 \), Identity Problems, \( t(14) = 6.17, p < .001 \), Cognitive Dysregulation, \( t(12) = 5.64, p < .001 \), and Insecure Attachment, \( t(14) = 6.19, p < .001 \). Additionally, the scales with the smallest differences between groups were those representing personality pathology thought to be unrelated to BPD: Compulsivity, Intimacy Problems, and Restricted Expression.

3.3 Neuroimaging Findings

3.3.1 Subsequent memory effect. A univariate whole-brain analysis of within-subject memory effects revealed a pattern of brain activation consistent with predictions when collapsing across groups. When contrasting BOLD responses obtained during the presentation of subsequently remembered scenes with scenes subsequently forgotten (‘remembered > forgotten’), significant clusters of activation (\( p < .05 \) FWE-corrected, cluster-forming threshold \( z = 2.30 \)) were observed in multiple regions (see Table 4 and Figure 2). Subsequently remembered scenes were associated with activity in the bilateral lateral occipital cortex (LOC), bilateral precuneus, bilateral temporal occipital fusiform, right middle inferior frontal gyrus, right hippocampus, and right posterior cingulate cortex (PCC). The reverse contrast (‘forgotten > remembered’) revealed greater activity in the bilateral frontal poles, precuneus, PCC, supramarginal gyrus, and middle frontal gyrus.

3.3.2 Subsequent memory between groups. An ROI univariate analysis focused on the bilateral hippocampus revealed significantly less activity in the right hippocampus for BPD patients than controls for the ‘remembered > forgotten’ contrast (\( p < .05 \) SVC, cluster-forming
threshold \( z = 2.30 \). The peak voxel was within the anterior region of the hippocampus (\( x = 32, \ -y = 14, \ z = -20 \)) and the observed difference in activity did not extend into posterior regions (See Figure 3). The mean activation in the area immediately surrounding the peak voxel (5mm sphere centred on the peak voxel) for each participant is visualized in Figure 4, and these individual estimates of hippocampal activation were used in symptom correlation analyses (described below). No significant differences in activation were observed in the left hippocampus and no differences in hippocampal activation were revealed by the ‘forgotten > remembered’ contrast (i.e. no areas of increased activation were observed for ‘remembered > forgotten’).

### 3.3.3 Relationship between hippocampal activation and symptom measures

No significant correlations were found between hippocampal activation (mean % signal change within 5mm of the peak comparison voxel between groups) and self-report measures. However, correlations were in the expected direction for BPD symptom severity (ZAN-BPD), \( r = -.31, p = .11 \), and perceived stress (PSS), \( r = -.22, p = 0.11 \). Medium to large effect size correlations were also observed for a number of DAPP-BQ dimensions with greatest relevance to BPD, including affective lability, \( r = -.51, p = .08 \), identity disturbance, \( r = -.42, p = .09 \), cognitive dysregulation, \( r = -.38, p = .10 \), and insecure attachment, \( r = -.38, p = .10 \). Only a weak correlation was observed between hippocampal activation and subjective memory function (MFQ), \( r = .08, p = .12 \).
**Chapter 4**

**Discussion**

This was the first study to examine how the neural circuitry underlying rudimentary memory encoding processes may be disrupted in BPD. Across groups, the principal within-subjects contrast (remembered > forgotten scenes) revealed a pattern of brain activity which suggested that the paradigm was successful at recruiting neural circuitry associated with memory encoding. To address the primary objective of this study, the hippocampal activation associated with successful memory encoding was compared between groups of BPD patients and age- and sex-matched non-psychiatric controls. Consistent with hypotheses, this contrast revealed significantly less activity in the right hippocampus in the patient group relative to controls, suggesting that memory encoding processes associated with this region may be disrupted. Correlations between right hippocampal activation and self-reported severity of symptoms and personality psychopathology were also explored, revealing non-significant small to large negative correlations across the measures.

The patterns of brain activation associated with subsequent remembering and forgetting are largely consistent with prior studies employing the same paradigm. In the present study, scenes which were successfully remembered were associated with clusters of activation in the bilateral lateral occipital cortex, precuneus, temporal occipital fusiform cortex (including the parahippocampal place area), the right middle inferior frontal gyrus, and the right hippocampus. All of these regions have all been associated with subsequent memory through meta-analyses of studies employing non-verbal memoranda (Kim, 2011) or paradigms specifically employing complex visual scenes (Chai, Ofen, Jacobs, & Gabrieli, 2010). Similarly, activation associated with subsequent forgetting in the present study was largely consistent with previous meta-
analyses (Kim, 2011). This included activation in bilateral frontal pole, precuneus, posterior parietal cortex, supramarginal gyrus, middle frontal gyrus, and right angular gyrus. Overall, observing the conventional patterns of activation observed for subsequently remembered and forgotten trials suggests that the paradigm employed in the present study was successful at engaging regions associated with memory encoding.

The differences in hippocampal activation between groups are also consistent with previous related work using neuroimaging to examine other memory-related processes associated with BPD. A reduction of left hippocampal activation in patients relative to controls was also reported by Soloff et al. (2015) during the encoding of negative and neutral versus positively valenced images. Whereas these results highlight the influence of emotional valence on hippocampal activation, the results of the present study speak more directly to the differences in encoding-related hippocampal functioning between patients and controls. Other neuroimaging findings related to memory in BPD explored brain activation during episodic and cued semantic recall or cued autobiographical memory retrieval, none of which revealed differences in hippocampal activation (Driessen et al., 2004; Mensebach et al., 2009; Schnell et al., 2007). Although not directly related to memory, the results of the present study are also somewhat consistent with earlier PET research which suggested that BPD may be associated with reduced left hippocampal metabolism at rest (Juengling et al., 2003).

One notable distinction between the results obtained in the present study and those reported by previous studies is the laterality of activation in certain regions associated with subsequent memory. Left hippocampal activation is typically associated with subsequent memory of verbal stimuli, while non-verbal (pictorial) stimuli tend to be associated with bilateral hippocampal activation (Kim, 2011). In the present study, which used complex visual scenes as
memoranda, activation in only the right hippocampus was associated with subsequent memory. Consequently, it is not surprising that differences in hippocampal activation between BPD patients and controls were limited to the right hippocampus, as the contralateral region did not appear to be activated by the task. In addition, right lateralized activation in the inferior frontal gyrus was associated with subsequent memory across groups, where only left-sided activation was reported in a prior meta-analysis (Kim, 2011). However, this lateralization of prefrontal activity is not surprising given the effect of stimulus modality on prefrontal activity demonstrated by previous research (Lee, Robbins, Pickard, & Owen, 2000; Wagner et al., 1998). The complex visual scenes used in this study may have been less likely to be internally verbalized by participants than simpler pictorial stimuli used by other studies. Consequently, left-lateralized regions typically associated with verbal processing may not have been strongly engaged during stimulus presentation. Alternatively, this right-lateralized pattern of activation may be due to the limited power of this relatively small sample, with the possibility that complex visual scenes produced a stronger effect in the right hemisphere than the left.

Stress has been shown to have a widespread influence on cerebral structure (Ganzel, Kim, Glover, & Temple, 2008) with the hippocampus shown to be a region especially sensitive to the deleterious effects of stress (Kim & Diamond, 2002). Consistent with prior research (Beblo et al., 2014; Ruocco et al., 2014), BPD patients in this sample reported perceiving significantly higher daily stress than controls during the previous month. Chronic stress is thought to reduce synaptic plasticity in the hippocampus due to the direct effect of stress hormones on the region and additional indirect effects mediated by the amygdala, a region thought to be hyperactive in BPD (Schulze, Schmahl, & Niedtfeld, 2016). Stress hormones, including cortisol, are released by the hypothalamic–pituitary–adrenal axis (HPA) in response to
stressful situations. Increased cortisol secretion and lower feedback sensitivity of the HPA axis have been associated with BPD (Lieb et al., 2004). Morphometric studies have suggested that chronic stress may produce a reduction in hippocampal grey matter (Gianaros et al., 2007), an anatomical feature also associated with BPD (Ruocco et al., 2012). The release of glucocorticoids (including cortisol) and other stress hormones released by the HPA axis are thought to suppress hippocampal long-term potentiation directly and through indirect effects mediated by the amygdala (Kim & Diamond, 2002). The reduced hippocampal activation observed in patients during successful memory encoding in the present study may be due to the downstream effects of chronic stress, which may alter the microstructure and associated functioning of the region. A nonsignificant small correlation, $r = -0.22, p = 0.11$, was observed across groups in the present study between perceived stress levels during the past month and right hippocampal activation.

Several limitations of this work should be considered when interpreting the results of the study. The first and primary limitation is the small sample size, which limits the inferences that can be drawn about how certain characteristics might have influenced the present findings. For example, individuals with BPD represent a largely heterogeneous sample with a variable constellation of comorbid diagnoses and treatment history. To capture this heterogeneity and ensure generalizability of results to the typical treatment-seeking patient with BPD, the patient sample included females with additional current and lifetime psychiatric diagnoses. However, with only eight patients retained in the final sample, this study did not have the statistical power to examine the potential associations of comorbid disorders with hippocampal activation during memory encoding. It would be especially interesting to examine how hippocampal activation may be associated with a comorbid diagnosis of PTSD, given that this disorder has also been
shown to impact hippocampal structure and function (Bremner, 2002). One may also overcome the limitations posed by diagnostic comorbidity in smaller samples by incorporating dimensional measures of psychopathology, allowing the relationships between relevant symptoms and outcome variables to be examined across all experimental groups.

An additional limitation to consider in the present study is that patients were not excluded from participation if they were currently taking one or more psychiatric medications. Although this was intended to allow further generalizability of the results to the typical treatment-seeking individual with BPD, it is possible that psychoactive medications may have altered brain activation patterns in the five patients currently undergoing pharmacological treatment. For example, some patients were taking anticonvulsant (n = 4) and/or antipsychotic medications (n = 3) at the time of participation, both of which may be expected to have some influence on brain activity (Delaveau et al., 2011; Matthew et al., 1995). A larger sample would have allowed examination of the possible influence of psychiatric medications on hippocampal activation, marking an important future direction of this research. Additionally, men with BPD were not considered in this study, limiting the generalizability of results. Given the lower prevalence of BPD in males compared to females (especially in treatment-seeking samples; Goodman et al., 2010), more research is needed to clarify possible sex differences in brain activation for patients and controls on the subsequent memory paradigm.

With increasing emphasis being placed on dimensional analyses and approaches consistent with the Research Domain Criteria (RDoC; Insel et al., 2010), a larger sample of patients and controls would allow sufficient power to examine the relationship between dimensional measures of personality and psychopathology on brain activation and serve to complement analyses based on the categorical BPD diagnosis. For example, cognitive
dysregulation or affective lability are core dimensions of BPD psychopathology (Gunderson et al., 2011; Ruocco, Hudson, Zanarini, & Gunderson, 2015) that could account for lower levels of hippocampal activation observed in BPD, which may have implications for understanding how these symptom dimensions operate in other mental disorders where they are prevalent. Additionally, if stress levels are found to be associated with hippocampal activation, the potential cognitive benefits of pharmacological treatments such as fluvoxamine, shown to modulate cortisol release in some BPD patients (Rinne et al., 2003), should be further explored. A number of promising trends were uncovered in this study sample with respect to dimensions of symptom severity (e.g. a strong but non-significant negative correlation between affective lability and subsequent memory-related hippocampal activation) but a greater number of patients and controls will be necessary to fully resolve these potential relationships.

Another promising future direction of this research would be to examine the relationship between hippocampal size and activity in the region during memory encoding. BPD patients have reduced hippocampal grey matter volume compared to non-psychiatric controls (Ruocco et al., 2012). It would be interesting to investigate whether reduced hippocampal activation during memory encoding may be a consequence of hippocampal structural differences, or whether the reduction in activity persists even after methodologically or statistically controlling for smaller hippocampal volumes. To approach this question, a future study could match for hippocampal size between patients and controls when comparing brain activation, ideally using a larger sample.

A more remote future direction stemming from this study would be to expand the scope of this research to include individuals with other mental disorders as additional clinical comparison groups. Subjective and objective memory disturbances are features of a number of
other disorders (Airaksinen, Larsson, & Forsell, 2005; Burdick, Endick, & Goldberg, 2005; Torres, Boudreau, & Yatham, 2007). It would be interesting to explore the possible similarities across these diagnoses in terms of encoding-related brain activation, potentially revealing common functional disturbances in memory circuitry. Additional, it would also be interesting to examine how dimensional measures of symptom severity or problems common to these disorders may be related to differences and similarities in brain activation across different patient groups that vary along a particular symptom dimension. It would also be useful to consider how closely these dimensions may map onto domains of research outlined in the RDoC framework, allowing the integration of future results into subsequent revisions of the RDoC matrix.

In conclusion, the present study marks the first attempt to explore the fundamental functional neural correlates of memory encoding in BPD. This was accomplished by employing a standard subsequent-memory fMRI paradigm and comparing hippocampal activation associated with subsequently remembered stimuli between age- and sex-matched BPD patients and non-psychiatric controls. Patients exhibited reduced activity in the right hippocampus, highlighting the possibility that disruptions at the level of encoding-related may underlie the memory disturbances associated with the disorder. This difference in brain activation underlying a process as primary as memory encoding provides preliminary evidence to suggest that the memory disturbances associated with BPD may not wholly not be due to emotional interference or impaired memory recall. Rather, this diminished hippocampal functioning associated with memory encoding may introduce a problem at an earlier stage that could disrupt or alter the formation of new memories. It is reasonable to expect that if there are disruptions in the initial processes of memory encoding that BPD patients would report day-to-day memory impairments and exhibit reduced performance on standardized tests of episodic memory. Further work will
help elucidate the relationship between this altered hippocampal activation, memory performance, stress, symptoms severity, and hippocampal structural features associated with BPD.
## Table 1.

Summary of diagnostic comorbidities within the final patient group.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>N</th>
<th>Percent in final sample</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major depressive disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>2</td>
<td>25%</td>
</tr>
<tr>
<td>Past</td>
<td>5</td>
<td>62.5%</td>
</tr>
<tr>
<td><strong>Dysthymic disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td><strong>Alcohol abuse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td><strong>Alcohol dependence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>1</td>
<td>37.5%</td>
</tr>
<tr>
<td><strong>Past Substance abuse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td><strong>Past Substance dependence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedative</td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td>Hypnotic</td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td>Opioid</td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td><strong>Substance induced psychotic disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td><strong>Panic Disorder with agoraphobia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td><strong>Panic Disorder without agoraphobia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td><strong>Social Phobia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td>Past</td>
<td>3</td>
<td>37.5%</td>
</tr>
<tr>
<td><strong>Obsessive-compulsive disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td><strong>Post-traumatic stress disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>2</td>
<td>25%</td>
</tr>
<tr>
<td>Past</td>
<td>2</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Generalized Anxiety Disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>3</td>
<td>37.5%</td>
</tr>
<tr>
<td><strong>Anorexia nervosa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>2</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Bulimia nervosa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>1</td>
<td>12.5%</td>
</tr>
<tr>
<td><strong>Binge Eating Disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>1</td>
<td>12.5%</td>
</tr>
</tbody>
</table>
Table 2.
Summary of group characteristic and task performance.

<table>
<thead>
<tr>
<th>Characteristic / measure of performance</th>
<th>Controls (n = 8)</th>
<th>Patients (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.63</td>
<td>8.33</td>
</tr>
<tr>
<td>Indoor/outdoor scene judgement accuracy</td>
<td>90.17%</td>
<td>3.83%</td>
</tr>
<tr>
<td>Reaction time to recognition memory probes (sec)</td>
<td>2.50</td>
<td>0.78</td>
</tr>
<tr>
<td>Number of scenes subsequently remembered</td>
<td>75.00</td>
<td>20.23</td>
</tr>
<tr>
<td>Number of scenes subsequently forgotten</td>
<td>75.00</td>
<td>20.23</td>
</tr>
<tr>
<td>D-prime for recognition memory performance</td>
<td>1.14</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Table 3.
Summary of group responses to self-report measures.

<table>
<thead>
<tr>
<th>Measure (select subscales)</th>
<th>Controls (n = 8)</th>
<th>Patients (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>ZAN-BPD</td>
<td>1.38</td>
<td>1.41</td>
</tr>
<tr>
<td>PSS</td>
<td>8.13</td>
<td>4.45</td>
</tr>
<tr>
<td>MFQ</td>
<td>312.00</td>
<td>52.19</td>
</tr>
<tr>
<td><strong>DAPP-BQ (percentile)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affective Lability</td>
<td>17.75</td>
<td>9.75</td>
</tr>
<tr>
<td>Identity Problems</td>
<td>35.38</td>
<td>26.82</td>
</tr>
<tr>
<td>Cognitive Dysregulation</td>
<td>29.25</td>
<td>15.21</td>
</tr>
<tr>
<td>Insecure Attachment</td>
<td>32.00</td>
<td>22.25</td>
</tr>
</tbody>
</table>

*Note. ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder, PSS = Perceived Stress Scale, MFQ = Memory Functioning Questionnaire, DAPP-BQ = Dimensional Assessment of Personality Pathology – Basic Questionnaire.*
Table 4.

Peak activation of clusters associated with remembered and forgotten scenes.

<table>
<thead>
<tr>
<th>Region</th>
<th>X(mm)</th>
<th>Y(mm)</th>
<th>Z(mm)</th>
<th>Peak signal intensity (z-score)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Remembered &gt; Forgotten</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Left</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral occipital cortex &amp; Precuneus</td>
<td>-42</td>
<td>-82</td>
<td>22</td>
<td>4.33</td>
</tr>
<tr>
<td>Temporal occipital fusiform gyrus</td>
<td>-30</td>
<td>-58</td>
<td>-14</td>
<td>4.06</td>
</tr>
<tr>
<td><strong>Right</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral occipital cortex</td>
<td>28</td>
<td>-72</td>
<td>36</td>
<td>4.90</td>
</tr>
<tr>
<td>Precuneus</td>
<td>10</td>
<td>-52</td>
<td>14</td>
<td>3.90</td>
</tr>
<tr>
<td>Posterior cingulate cortex</td>
<td>12</td>
<td>-46</td>
<td>2</td>
<td>3.38</td>
</tr>
<tr>
<td>Temporal occipital fusiform gyrus</td>
<td>26</td>
<td>-42</td>
<td>-18</td>
<td>4.26</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>22</td>
<td>-16</td>
<td>-18</td>
<td>3.46</td>
</tr>
<tr>
<td>Middle inferior frontal gyrus</td>
<td>46</td>
<td>18</td>
<td>28</td>
<td>4.42</td>
</tr>
<tr>
<td><strong>Forgotten &gt; Remembered</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Left</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>-48</td>
<td>-48</td>
<td>38</td>
<td>3.53</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>-36</td>
<td>34</td>
<td>34</td>
<td>3.33</td>
</tr>
<tr>
<td>Frontal pole</td>
<td>-24</td>
<td>44</td>
<td>14</td>
<td>3.77</td>
</tr>
<tr>
<td><strong>Bilateral</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precuneus</td>
<td>8</td>
<td>-60</td>
<td>38</td>
<td>3.76</td>
</tr>
<tr>
<td>Posterior parietal cortex</td>
<td>0</td>
<td>-20</td>
<td>44</td>
<td>3.74</td>
</tr>
<tr>
<td><strong>Right</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angular gyrus</td>
<td>48</td>
<td>-58</td>
<td>38</td>
<td>3.71</td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>58</td>
<td>-42</td>
<td>48</td>
<td>3.95</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>42</td>
<td>28</td>
<td>36</td>
<td>3.52</td>
</tr>
<tr>
<td>Frontal pole</td>
<td>38</td>
<td>44</td>
<td>24</td>
<td>3.47</td>
</tr>
<tr>
<td>Frontal pole</td>
<td>18</td>
<td>60</td>
<td>20</td>
<td>3.54</td>
</tr>
<tr>
<td>Frontal pole</td>
<td>24</td>
<td>62</td>
<td>-2</td>
<td>3.54</td>
</tr>
</tbody>
</table>
Figure 1. Behavioural paradigm.
Figure 2. Regions of brain activation associated with subsequent memory (red) and subsequent forgetting (blue) across groups. Horizontal slice orientation, radiological convention (left is right), rendered on the MNI152 standard template ("z" refers to MNI coordinate), threshold at $p < 0.05$, F corrected for familywise error rate.
Figure 3. Hippocampal deactivation in patients compared to controls for remembered > forgotten scenes. Axial (left), sagittal (center), and horizontal (right) slice orientation, rendered on the MNI152 standard template (“x, y, z” refer to MNI coordinates), threshold at $p < 0.05$, corrected for familywise error rate, “R” = right, “L” = left, “S” = superior, “I” = inferior, “A” = anterior, “P” = posterior.

Figure 4. Mean hippocampal % signal change within 5mm of the peak comparison voxel.
References


memory in patients with borderline personality disorder. *Biol Psychiatry, 55*(6), 603-611. doi: 10.1016/j.biopsych.2003.08.018


43


Rey, A. (1944). Rey-Osterrieth Complex Figure Test. *Lutz, FL: Psychological Assessment Resources.*

with a history of sustained childhood abuse. *Neuropsychopharmacology, 28*(1), 126-132. doi: 10.1038/sj.npp.1300003


Spaniol, J., Davidson, P. S., Kim, A. S., Han, H., Moscovitch, M., & Grady, C. L. (2009). Event-related fMRI studies of episodic encoding and retrieval: meta-analyses using activation
likelihood estimation. *Neuropsychologia, 47*(8-9), 1765-1779. doi: 10.1016/j.neuropsychologia.2009.02.028


