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Examining Neural Correlates of Psychopathology Using a Lesion-Based Approach

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Abstract

Studies of individuals with focal brain damage have long been used to expand understanding of the neural basis of psychopathology. However, most previous studies were conducted using small sample sizes and relatively coarse methods for measuring psychopathology or mapping brain-behavior relationships. Here, we examined the factor structure and neural correlates of psychopathology in 232 individuals with focal brain damage, using their responses to the Minnesota Multiphasic Personality Inventory-2-Restructured Form (MMPI-2-RF). Factor analysis and voxel-based lesion symptom mapping were used to examine the structure and neural correlates of psychopathology in this sample. Consistent with existing MMPI-2-RF literature, separate internalizing, externalizing, and psychotic symptom dimensions were found. In addition, a somatic dimension likely reflecting neurological symptoms was identified. Damage to the medial temporal lobe, including the hippocampus, was associated with scales related to both internalizing problems and psychoticism. Damage to the medial temporal lobe and orbitofrontal cortex was associated with both a general distrust of others and beliefs that one is being personally targeted by others. These findings provide evidence for the critical role of dysfunction in specific frontal and temporal regions in the development of psychopathology.

Keywords

emotion; personality; voxel-based lesion symptom mapping; MMPI-2-RF

1. Introduction

Beginning in the early 1980s, advances in neuroimaging have been used to study psychopathology by comparing individuals with and without a psychiatric diagnosis (e.g., Andreasen, 1988; Gur et al., 1984). Research on the neural correlates of psychopathology has since been dominated by the approach of studying patients with specific diagnoses separately despite a high degree of comorbidity across disorders (Synder, Hankin, Sandman,

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& Davis, 2017). It is possible that findings thought to be specific to an individual disorder may instead reflect broader dimensions of psychopathology (Zald & Lahey, 2017). In line with this view, meta-analyses of individual disorders have yielded partially overlapping findings across a number of brain regions that can be broadly considered as part of an extended fronto-limbic system. For example, in examining the overlap across studies of psychotic and nonpsychotic disorders, reduced grey matter was found in the insula and anterior cingulate cortex (ACC) in patients with psychosis, compared to those without a diagnosis (Goodkind et al., 2015). Examining individual meta-analyses of disorders as diverse as schizophrenia, depression, and post-traumatic stress disorder yields commonalities such as reduced volumes in the medial temporal lobe (e.g., amygdala and hippocampus) as well as the temporal lobe more broadly (e.g., see reviews by Bora et al., 2011, Bora, Fornito, Pantelis, & Yücel, 2012, Karl et al., 2006, Kühn & Gallinat, 2013). In the past few years especially, some studies have examined the neural correlates of broad dimensions of psychopathology. For example, in one study of children, reductions in prefrontal cortex volume were associated with psychopathology in general, but reductions in the volume of limbic regions, including the amygdala and hippocampus, were associated specifically with internalizing symptoms (Synder et al., 2017).

These findings of an association between psychopathology and medial temporal lobe volume parallel findings in the personality neuroscience literature. Trait neuroticism, which is robustly associated with many categories of psychopathology (Kotov, Gamez, Schmidt, & Watson, 2010), is associated with reduced medial orbitofrontal cortex volume and increased amygdala volume (Mincic, 2015). Neuroticism has also been linked to altered connectivity between the amygdala and prefrontal cortex which may reflect its relationship to emotional regulation (Abram & DeYoung, 2017; Mincic, 2015). Compared to neuroticism, other personality traits have been less widely studied, and the use of small studies is likely a contributor to the heterogeneity of findings for other traits (Abram & DeYoung, 2017). Some of the more consistent findings are positive associations between extraversion and ventromedial prefrontal cortex volume, and conscientiousness and lateral prefrontal cortex volume (Allen & DeYoung, 2017). Also, reduced volume in the orbitofrontal cortex has been linked to externalizing disorders (e.g., Ersche, Williams, Robbins, & Bullmore, 2013; Yang & Raine, 2010) and also the related personality trait of impulsivity (e.g., Matsuo et al., 2009). Psychopathy, a disorder involving impaired emotional processing and impulsivity (among other things), has been linked to reduced anterior temporal lobe, medial temporal lobe, and orbitofrontal volumes (Ermer, Cope, Calhoun, Nyalakanti, & Kiehl, 2012; Oliveira-Souza et al., 2007). A recent study of over 500 participants in the Human Connectome Project (HCP) found differing associations between gray matter and personality depending on the metric used (i.e., cortical thickness, surface area, or cortical folding) (Riccelli, Toschi, Nigro, Terracciano, & Passamonti, 2017). This study replicated well established associations (e.g., neuroticism and frontal and temporal regions), and also reported some more novel relationships, but in general, results emphasized the importance of prefrontal cortex measures to individual differences in personality.

Although some findings have been reproduced across studies, concerns have been raised about the high prevalence of small, underpowered studies in both psychopathology and personality research (Fusar-Poli et al., 2014; Yarkoni, 2013). Furthermore, differences

between participants with diagnosed psychopathology and comparison participants without diagnosed psychopathology may reflect confounds such as medication or substance use (Weinberger & Radulescu, 2016). The reliance on diagnostic comparisons in many studies also brings about broader issues related to categorical diagnoses (e.g., large within-disorder variation in symptoms) that make the identification of biological correlates challenging (Kozak & Cuthbert, 2016). For example, in one study of approximately 3,700 patients diagnosed with major depressive disorder, when depressive symptoms were classified as either present or absent to yield symptom profiles, the most common profile was present in only 1.8% of patients (Fried & Nesse, 2015). Moreover, different symptoms or clusters of symptoms within major depressive disorder have different genetic correlates (e.g., Milaneschi et al., 2016) and risk factors (e.g., Fried, Nesse, Zivin, Guille, & Sen, 2014).

The lesion method is a time-honored approach to studying brain-behavior relations. The approach is based on associations between focal neural damage and specific behavioral deficits, and it has a critical advantage (especially relative to functional neuroimaging approaches, such as fMRI) in assessing the neural correlates of psychopathology. Specifically, the lesion method can provide a more definitive test of the necessity of specific brain regions for a behavior (e.g., Poldrack & Farah, 2015). The lesion method has been used previously to delineate relationships between brain systems and specific psychological symptom dimensions (e.g., cognitive/affective vs. somatic symptoms that occur in depression; Koenigs et al., 2008). It has also been used to test etiological theories of psychopathology such as the role of fearlessness in psychopathy (by showing that focal amygdala damage resulting in fearlessness is not associated with affective features of psychopathy such as a lack of empathy or feelings of guilt; Lilienfeld et al., 2016). The expression of psychopathology in patients with brain damage can be very similar to that seen in patients with psychiatric disorders, and this has provided rationale for studying the neural correlates of psychopathology in both patients with focal lesions and patients with other neurological diseases (e.g., Alzheimer's disease and other progressive dementias) (Levenson, Strum, & Haase, 2014).

Many lesion studies have used relatively coarse methods to classify brain damage and its relationship to behavior. Studies have tended to rely on categorical approaches; for example, creating a limited number of coarse groups of patients based on the location of their brain damage or dichotomizing continuous behavioral data (e.g., test scores) as either impaired or unimpaired. Techniques are now available that overcome some of these limitations (Bates et al., 2003; Pustina, Avants, Faseyitan, Medaglia, & Coslett, 2017; Rorden & Karnath, 2004). For example, voxel-based lesion symptom mapping (VLSM) allows for the examination of differences on a dependent measure (e.g., score on a self-report measure) on a voxel-by-voxel basis, in a manner parallel to the method in which functional neuroimaging data are often examined (Bates et al., 2003; Rorden & Karnath, 2004). This method can improve the accuracy, precision, and power of lesion-based analyses. Also, voxel-based lesion symptom mapping allows for the opportunity to examine neural correlates of psychopathology using dimensional measures. Dimensional measures of psychopathology on average have greater reliability and validity than categorical measures (Markon & Chmielewski, 2011). Furthermore, dimensional assessment is aligned with hierarchical models of psychopathology (e.g., internalizing/externalizing: Krueger & Markon, 2006; internalizing/

externalizing/psychosis: Wright et al., 2013) which have strongly influenced the Research Domain Criteria (RDoC) initiative (Kozak & Cuthbert, 2016) and may be a useful framework for examining the biological correlates of psychopathology (Krueger & DeYoung, 2016; Nikolas, Markon, & Tranel, 2016).

One broadband, dimensional measure of psychopathology is the Minnesota Multiphasic Personality Inventory (MMPI) and its subsequent iterations (i.e., the Minnesota Multiphasic Personality Inventory-2nd Edition (MMPI-2) and Minnesota Multiphasic Personality Inventory-2-Restructured Form (MMPI-2-RF)). These measures are among the most widely used personality tests in clinical psychology and neuropsychology (Camara, Nathan, & Puente, 2000). In recent surveys, MMPI-2 and MMPI-2-RF ranked as the measures of personality and psychopathology most widely taught to clinical psychology doctoral students (Mihura, Roy, & Graceffo, 2016). Also, versions of the MMPI are the most frequently used measures of psychopathology and personality administered by clinical neuropsychologists (Rabin, Paolillo, & Barr, 2016). The latest version of the MMPI, the MMPI-2-RF, was designed to be aligned with contemporary conceptualizations of psychopathology and includes a hierarchical structure with measures of three factors of psychopathology (i.e., internalizing, externalizing, and psychotic symptoms), a five-factor personality trait model that overlaps significantly with the alternative DSM-5 trait model for personality disorders (Anderson, Sellbom, Bagby, Quilty, Veltri, Markon, & Krueger, 2013; Harkness et al., 2014), and scales designed to capture the major constructs assessed by the original MMPI clinical scales (e.g., somatic concerns for the original Hypochondriasis scale) (Ben-Porath, 2012).

In the study reported here, we used exploratory factor analysis and voxel-based lesion symptom mapping (VLSM) to examine the structure and neural correlates of a reasonably comprehensive set of psychopathology constructs as measured by the MMPI-2-RF in a large sample of individuals with focal brain damage. Prior to conducting our lesion analyses, we examined the factor structure of the restructured clinical scales in our sample. We do not know of previous large-scale studies of the factor structure of MMPI-2-RF scales in individuals with focal brain damage, and prior to examining individual scales, we wanted to examine their construct validity in this unique sample. Given robust findings of similarities in personality and psychopathology structure across various clinical and nonclinical samples (e.g., O'Connor, 2002), we hypothesized that, consistent with the MMPI-2-RF literature (e.g. Ben-Porath & Tellegen, 2008), a three factor structure of the MMPI-2-RF RC scales would be obtained, reflecting separate internalizing, externalizing, and psychoticism dimensions. Given the dominance of studies examining diagnostic groups rather than symptoms per se, a hybrid confirmatory and exploratory research strategy was employed in regards to hypothesis testing of neural correlates. Based on prior research in non-lesion samples, it was hypothesized that internalizing and psychotic symptoms (e.g., RC7 (Dysfunctional Negative Emotions) and RC8 (Aberrant Experiences)) would be associated with medial temporal lobe damage while externalizing symptoms (e.g., RC9 (Hypomanic Activation)) would be associated with orbitofrontal damage. Given the widespread use of the MMPI-2-RF and the breadth of psychopathology constructs it assesses, an exploratory approach was also used to maximize the benefit of VLSM to uncover brain-behavior relationships that could inform research on the biological basis of psychopathology. We

explored the full set of MMPI-2-RF Restructured Clinical (RC) and Personality Psychopathology Five–Revised (Psy-5-r) scales using a whole brain approach.

2. Method

2.1. Participants

A large number of individuals (N=232) with focal brain lesions were administered either the original MMPI (n=41) or MMPI-2 (n=191) in conjunction with their participation in the Iowa Neurological Patient Registry in the Department of Neurology at the University of Iowa. Etiologies for brain damage included ischemic stroke (n = 92), temporal lobe resection as a treatment for epilepsy (n = 49), hemorrhagic stroke or related surgical intervention (e.g., arteriovenous malformation (AVM) resection or aneurysm clipping; n = 43), benign tumor resection (n = 34), herpes simplex or other encephalitis (n = 5), head trauma with focal contusion (n = 5), and other causes (e.g., Urbach-Wiethe Disease, cysts; n = 4). The average age at time of testing for all participants in this study was 50.0 years (SD = 15.2). The average level of education of the sample was 13.8 years (SD = 2.8). 50.4% of the sample was female (n = 117). Testing was completed in the chronic epoch of recovery, at least 3 or more months after lesion onset, with an average of 5.83 years between lesion onset and completion of the MMPI or MMPI-2 (Range: 6 months to 35 years). Nearly all participants identified as Caucasian (n = 224) with remaining participants identifying as African American (n = 3), American Indian (n = 2), or some other unspecified race (n=3). 88.8% (n = 206) of participants were predominately right-handed, 7.8% (n = 18) were predominately left-handed, and 3.4% (n=8) were mixed-handed. Participants were assessed for adequate reading comprehension with the Multilingual Aphasia Examination (MAE) Reading Comprehension of Words and Phrases subtest (Benton, Hamsher, Rey, & Sivan, 1994) or Wide Range Achievement Test 4 (WRAT4) Word Reading and Sentence Comprehension subtests (Wilkinson & Robertson 2006) prior to completing the MMPI or MMPI-2; 10 patients were excluded for poor reading comprehension. Participants were also assessed by a clinical psychologist prior to induction into the Patient Registry, and only those not diagnosed or treated for a psychiatric disorder at the time of lesion onset were enrolled (premorbid psychiatric illness is a longstanding exclusion criterion for induction into our Patient Registry more generally). This allows for a more robust conclusion of symptom elevations being related to the lesion rather than pre-morbid psychopathology. All participants gave written informed consent to have their test data used for ongoing research studies and this process was approved by the Institutional Review Board of the University of Iowa.

Participants' responses on either the original MMPI or MMPI-2 were recoded to MMPI-2-RF scoring. Missing data (e.g., due to the administration of the abbreviated 370-item form of the MMPI-2 or an MMPI-2-RF item not present on the original MMPI) were imputed on a scale-by-scale basis for each participant; participants' mean scores on the completed items were used to estimate their responses to the items they did not complete. Data from participants were excluded for a scale if the amount of available data for that scale was less than 50% of the total items on the scale. This led to an average of 1% of participants not being used for a scale with at most 5% of participants not used for an individual scale. A

large amount of complete data was available with on average 90% of items complete across scales. However, across scales, an average of 34% of participants required at least some imputation, with the average amount of imputation done ranging from 4 to 44%. Although prorating based on abbreviated protocols has previously not been reported in the literature, a prorating approach has been previously used by MMPI-2-RF researchers to convert data from full administrations of the original MMPI (i.e., Tarescavage, Corey, & Ben-Porath, 2015). Raw scores were converted to T-scores based on the MMPI-2-RF normative sample (Tellegen & Ben-Porath, 2008). Scores from the Restructured Clinical (RC) scales and Personality Psychopathology Five–Revised (Psy-5-r) scales were used in the analyses. Scale means are presented in Supplemental Table S1.

2.2. Data Analysis

2. 2.1 Exploratory Factor Analysis—To investigate whether the MMPI-2-RF scales measure the same constructs in neurological patients with focal brain lesions as they do in patients with psychiatric disorders, the Restructured Clinical scales were analyzed using exploratory factor analysis with an oblique geomin rotation. To be consistent with prior investigations of the MMPI-2-RF factor structure (e.g., Hoelzle & Meyer, 2008; Selbom, Ben-Porath, & Bagby, 2008), item parcels from each scale, rather than scale totals or individual items, were used. Parallel analysis was used to determine the number of factors to estimate (Glorfield, 1995).

2.2.2. Statistical Lesion Analysis—Lesions were manually traced from structural MR or CT scans onto a standardized brain template using the MAP-3 method (Fiez, Damasio, & Grabowski, 2000; Frank, Damasio, & Grabowski, 1997). Voxel-based lesion symptom mapping (VLSM) was used to identify significant relationships between MMPI-2-RF scores and brain damage (Bates et al., 2003; Rorden, Karnath, & Bonilha, 2007). Separate VLSM analyses were run for each MMPI-2-RF scale. At each voxel, the scores of patients with and without a lesion to that voxel were compared using the Brunner-Munzel test (Brunner & Munzel, 2000). Significant voxels ($p<0.05$) are those in which patients with damage at that voxel had significantly higher scores than patients without damage at that voxel, using the B-M statistic and controlling for multiple comparisons with the false discovery rate. Only voxels in which at least 2% of the sample had damage were included in the analysis; this was done so that only those voxels in which at least 4 patients had damage were included, a threshold used in prior VLSM studies (e.g., Gläscher et al., 2009; Knutson et al., 2014). Statistical power maps were generated to illustrate regions with and without power to detect significant effects. Analyses were performed using the “Nonparametric Mapping” function in MRIcron (Rorden, Karnath, & Bonilha, 2007). Rather than excluding patients with elevations on validity scales, all patients were included in all analyses, and validity scales were examined individually in VLSM analyses.

3. Results

3.1. Exploratory Factor Analysis of the Restructured Clinical Scales

Parallel analyses indicated that four factors should be estimated. The first five eigenvalues from the actual data were 9.15, 2.82, 1.79, 1.54, 1.30 and the corresponding first five 95th

percentile random data eigenvalues were 1.79, 1.65, 1.57, and 1.50, and 1.43. This model had adequate model fit (CFI = 0.90, RMSEA = 0.07, SRMR = 0.04) (Hu & Bentler, 1999). The estimated four factor model largely reflected separate internalizing (i.e., RCd: Demoralization, RC2: Low Positive Emotions, and RC7: Dysfunctional Negative Emotions), psychoticism (i.e., RC6: Ideas of Persecution and RC8: Aberrant Experiences), and externalizing (i.e., RC3: Cynicism, RC4: Antisocial Behavior, and RC9: Hypomanic Activation) factors, with an additional factor consisting only of somatic concerns (i.e., RC1: Somatic Complaints). Factor loadings are shown in Supplemental Table S2.

3.2. Statistical Lesion Analyses

Statistical power maps generally showed adequate power to detect signification lesion-symptom relationships throughout most of the brain, with the exception of some areas within the occipital lobe and the most superior portions of the frontal and parietal lobes (See Supplemental Figures S1–S3). Areas in red denote regions in which there is adequate power to detect a difference based on the 5% false discovery rate (FDR). Power is a function of the lesion overlap distribution; the maximum possible z-score that would be obtained if all patients with lesions at an individual voxel had the highest MMPI-2-RF scores is compared to the FDR-corrected threshold. The distribution of power obtained for MMPI-2-RF scales reflects those brain regions that are most often clinically affected by brain injury (e.g., regions supplied by the middle cerebral artery, the most common site of stroke (Bogousslavsky, Van Melle, & Regli, 1988)). The non- or under-sampled regions in our population are common in lesion work, due to the rarity of naturally occurring lesions in these areas. Supplemental Figure 4 shows the lesion-overlap map for the entire sample.

3.2.1. MMPI-RF Restructured Clinical Scales and Validity Scales—Significant lesion-symptom mapping results for the MMPI-2-RF RC and validity scales are shown visually in Figure 1 and descriptively by cluster size and location in Table 1. Several RC scales were associated with specific voxels. Higher scores on the RC3 (Cynicism) scale were associated with left ventromedial prefrontal cortex/orbitofrontal cortex and left medial temporal lobe damage. Higher scores on the RC6 (Ideas of Persecution) scale were associated with left orbitofrontal and left medial and anterior temporal lobe damage, including the amygdala and hippocampus. Higher scores on the RC7 (Dysfunction Negative Emotions) scale were associated with left medial and anterior temporal lobe damage (including hippocampus) and right lateral temporal damage. Higher scores on the RC8 (Aberrant Experiences) scale were associated with left medial temporal damage, including the hippocampus and amygdala, and anterior left temporal lobe damage. The remaining Restructured Clinical scales – RCd (Demoralization), RC1 (Somatic Complaints), RC2 (Low Positive Emotions), RC4 (Antisocial Behavior), and RC9 (Hypomanic Activation) – were not significantly associated with damage to specific voxels. Only one MMPI-2-RF validity scale was significantly associated with damage: higher scores on the MMPI-2-RF Fs (Infrequent Somatic Response) Scale were significantly associated with damage to the left anterior temporal lobe.

3.2.2. MMPI-RF Revised Personality Psychopathology Five Scales—Significant lesion-symptom mapping results for the MMPI-2-RF Psy-5 scales are shown visually in

Figure 2 and descriptively by cluster size and location in Table 2. Two revised personality-psychopathology scales were associated with damage to specific voxels. Higher scores on the PSYC-r scale (Psychoticism-Revised) were associated with left medial temporal damage (including the hippocampus) and left temporal pole damage. Higher scores on the NEGE-r scale (Negative Emotionality/Neuroticism-Revised) were associated with left anterior temporal lobe damage. The remaining PSYC-r Scales, AGG-R (Aggressiveness-Revised), DISC-r (Disconstraint-Revised), and INTR-r (Introversion-Revised), were not significantly associated with damage to specific voxels.

4. Discussion

The present work builds on past studies of psychopathology in patients with focal brain damage, taking advantage of recent methodological and statistical improvements and a large sample of patients. Although functional neuroimaging approaches (especially fMRI) have become commonplace, lesion approaches retain the compelling inferential advantage of identifying brain regions that are necessary for a behavior (Bates et al., 2003, Rorden & Karnath, 2004). We used a lesion-based approach to examine the factor structure and neural correlates of dimensions of psychopathology as measured by the MMPI-2-RF, a widely used and extensive self-report measure of psychopathology and personality functioning.

4.1. Structure of Psychopathology

In contrast to previous versions of the MMPI, the scales on the MMPI-2-RF were derived using factor analytic techniques and can be interpreted separately as measures of specific symptom dimensions (Tellegen & Ben-Porath, 2008). As we did not know of previous large-scale studies of the factor structure of MMPI-2-RF scales in individuals with focal brain damage, we first examined the factor structure in our sample prior to conducting our lesion-based analyses.

The factor solution obtained largely yielded the same essential structure as prior results based on individuals with psychiatric disorders, with separate internalizing, externalizing, and psychoticism factors (Sellbom, Ben-Porath, & Bagby, 2008; Tellegen & Ben-Porath, 2008). In addition to being supported by MMPI research, this model of psychopathology has been found in studies using diagnostic interviews (Wolf et al., 1988; Wright et al., 2013). Prior work has suggested that the structure of measures of personality and psychopathology is generally robust across clinical and non-clinical groups (O'Connor, 2002). These findings extend that conclusion to the MMPI-2-RF and neurological patients with focal brain lesions specifically, and provide evidence for the construct validity of the MMPI-2-RF in this population. An exception to previous results was the presence of a fourth factor consisting only of somatic symptoms. However, there are some models of psychopathology which treat somatic symptoms as separate from internalizing symptoms (e.g., Kotov et al., 2017). Additionally, in contrast to prior MMPI-2-RF analyses, this finding may have been driven by physical symptoms present in neurological diseases separate from psychological distress or preoccupation with somatic concerns; the latter would be more likely associated with internalizing symptoms. Of note, the scale averages for nearly all clinical and personality scales were close to the mean of the normative sample, with the exception of nearly one

standard deviation elevation on RC1 (Somatic Complaints). This finding is consistent with several studies identifying increased endorsement of certain somatic items in neurological populations that reflect genuine cognitive or physical symptoms (e.g., Alfano, Finlayson, Stearns, & Neilson, 1990; Gass, 1992). The moderate RC1 elevation found here is in a range consistent with genuine health problems rather than a psychological preoccupation with health concerns or somatization (Ben-Porath, 2012). The lack of elevations on remaining MMPI-2-RF scales in the overall sample suggests that there is no general association of brain damage and psychopathology.

4.2. Neural Correlates of Psychopathology

Specific associations were found between damage to particular regions and elevations on MMPI-2-RF scales. It is important to note; however, that the average elevations for a region were relative elevations compared to those without damage in the same region rather than elevations in the clinical range of MMPI-2-RF interpretation. Therefore, findings reflect relative differences within a dimensional approach to psychopathology rather than scores traditionally associated with clinical diagnoses. Higher scores on scales assessing positive psychotic symptoms were associated with anterior, lateral, and, consistent with the hypotheses, medial temporal lobe damage. This association between the temporal lobe and psychosis has been observed frequently in neuroimaging studies of individuals with psychotic disorders. A meta-analysis of neuroimaging studies of schizophrenia identified the superior temporal gyrus and amygdala as two regions with reduced gray matter in individuals with the disorder compared to those without (Bora et al., 2011). Also, a reduction in hippocampal volume appears to be a robust finding across specific psychotic disorder diagnoses (Mathew et al., 2014). Temporal lobe epilepsy with psychosis can be distinguished from temporal lobe epilepsy without psychosis by patterns of reductions in gray matter in the regions of the temporal lobe (Sundram et al., 2010).

Higher scores on scales assessing anxiety and irritability were associated with anterior, lateral, and, consistent with the hypothesis, medial temporal lobe damage. This association is consistent with neuroimaging studies of individuals with anxiety disorders. Reductions in volume in the lateral temporal lobe were found in a heterogeneous group of individuals with different anxiety disorder diagnoses (i.e., panic disorder, social anxiety disorder, and generalized anxiety disorder; van Tol et al., 2010). Post-traumatic stress disorder, a disorder characterized in part by symptoms of anxiety, arousal, and reactivity, including irritability, has been associated with reduced hippocampal volume (Karl et al., 2006). Reductions in medial temporal lobe volume have also been associated with greater trait neuroticism in individuals without a clinical disorder (e.g., DeYoung et al., 2010). Neuroticism has also been associated with activation of the hippocampus during tasks of emotional processing (Servaas, van der Velde, Costafreda, Horton, Ormel, Riese, & Aleman, 2013). The role of medial temporal lobe structures (including the amygdala and hippocampus) in anxiety is consistent with animal research (Lang, Davis, Ohman, 2000), including studies of rhesus monkeys (e.g., Oler et al., 2010) and rats (e.g., Qi, Roseboom, Nanda, Lane, Speers, & Kalin, 2010).

In our study, not all scales associated with externalizing psychopathology were associated with damage to the orbitofrontal cortex, but partially consistent with our hypotheses, higher scores on scales assessing mistrust and suspiciousness of other's motives were associated with damage to the orbitofrontal cortex. Similar findings have been reported in prior structural neuroimaging studies. Behavioral and self-report measures of trust, the size of one's social network, and one's ability to infer the mental states of others are all associated with increased volumes in orbitofrontal cortex (Haas, Ishak, Anderson, & Filkowski, 2015; Lewis, Rezaie, Brown, Roberts, & Dunbar, 2011; see also Koscik & Tranel, 2012). Individuals with damage to these regions are less trusting in economic decision making games in which they are told they are interacting with another participant (Krajbich, Adolphs, Tranel, Denburg, & Camerer, 2009). Interestingly, elevated scores on a measure assessing feelings of being personally targeted by others was associated with both orbitofrontal and temporal cortex damage; reduced thickness in both of these regions is associated with paranoid delusions in Alzheimer's disease (Whitehead et al., 2012).

Our analyses examined associations between specific voxels and psychopathology. Although research linking specific brain regions to psychopathology continues to be published, a growing number of studies have focused on the role of structural and functional networks in psychopathology (e.g., McTeague, Huemer, Carreon, Jiang, Eickoff, & Etkin, 2017; Huchuan et al., 2017). Findings support a role of the central executive network, salience network, and default mode network in many disorders (Menon, 2011). Aberrant relationships among these networks have also been linked to psychopathology, with connections involving frontal and temporal regions found most consistently affected across different dimensions of psychopathology (e.g., Huchuan et al., 2017). A focus on networks may explain the heterogeneity of findings in other areas. For example, individual studies of the relationship between Alzheimer's disease and psychopathology are somewhat variable in their findings, but when examined together, regions within either the frontal cortex or so-called "limbic system" are most consistently associated with symptoms (Boublay, Schott, & Krolak-Salmon, 2016; Alyes et al., 2017). This may reflect dysfunction or disconnection in networks involving these regions.

Goodkind et al. (2015) identified the anterior cingulate and insula as regions with reduced volume across psychiatric disorders, and the investigators linked these regions to cognitive control based patterns of functional activation and task-performance in healthy participants. However, Goodkind et al. noted that the anterior cingulate is also involved in the salience network, which includes the amygdala, and is involved in both cognitive and emotional processing (Menon, 2015). Reduced amygdala volume was identified as being associated with psychopathology in Goodkind et al. (2015); reductions were noted when comparing internalizing vs. externalizing disorders and psychotic vs. non-psychotic disorders. Research broadly supports a role for damage or dysfunction in regions and networks associated with either cognitive control or emotions with psychopathology (Beauchaine & Zisner, 2017; Cole, Repovš, & Anticevic, 2014). Connectivity between these systems is associated with both symptoms of psychopathology and cognitive functioning (e.g., Alnæs et al., 2018) and with the development of symptoms over time (Marusak, Thomason, Peter, Zundel, Elrahal, & Rabinak, 2016). Animal research also has highlighted the importance of connectivity between regions in the prefrontal cortex and medial temporal lobe in psychopathology,

specifically for anxiety (Kalin, & Shelton, 2003). Techniques exist to apply network approaches to examining brain-behavior relationships in individuals with focal brain damage (e.g., Boes et al., 2015; Sutterer, Bruss, Boes, Voss, Bechara, & Tranel, 2016), applying such approaches in future studies may identify additional brain regions (e.g., in prefrontal lobes) associated with psychopathology not identified using a VLSM approach.

4.3. Strengths and Limitations

This study includes a large sample of individuals with focal brain damage who were not diagnosed with or being treated for a psychiatric condition at the time of their lesion onset. Although there are several prior lesion studies of the MMPI, those studies examined patterns of scale scores using a coarse group-based approach (e.g., individuals with “right hemisphere” vs. “left hemisphere” damage) and often relied on small samples including individuals with either acute or chronic lesions (e.g., Andersen & Hanvik, 1950; Dikmen & Reitan, 1977). In contrast, the current study is the first to use fine-grained methods (i.e., voxel-based lesion-symptom mapping) with scores from most recent adaptation of the MMPI obtained from a large sample of individuals in the chronic epoch of recovery from brain damage. The scales on the restructured form of the MMPI are less heterogeneous in content than the previous MMPI scales and have greater divergent validity in their relationship with psychiatric disorders (Simms, Casillas, Clark, Watson, & Doebbeling, 2005). To our knowledge, ours is the first comprehensive analysis of psychopathology symptoms assessed dimensionally in a large sample of patients with focal brain lesions. One previous study (e.g., Huey et al., 2015) used a limited set of clinical diagnoses and specific measures of depression and anxiety collected in a large sample of individuals with penetrating head injuries. Although that study also found a relationship between “limbic” structures and psychopathology, the specific findings did not overlap entirely with those of our study. However, given numerous methodological differences, including the use of a region-of-interest rather than voxel-based analysis, it is difficult to make direct comparisons.

A possible limitation in our study is the treatment of voxels in the VLSM method as independent. There has been a recent criticism of this methodological assumption due the effect of common etiologies (e.g., middle cerebral artery strokes) on co-occurrence of damage across voxels (Mah, Husain, Rees, & Nachev, 2014). However, in the current study, significant results were often found in regions with damage resulting from multiple different etiologies, lessening the effect of violating this assumption. For example, majority of associations were found between MMPI-2-RF scores and temporal lobe damage; the group of patients with temporal lobe damage included those with diverse etiologies resulting in varying degrees and distributions of brain damage: temporal lobectomies, benign tumor resections, and both ischemic and hemorrhagic strokes. Given the large sample size and distribution of lesions, the statistical power maps showed adequate power to detect significant relationships in many brain regions; however, this was not true of all brain regions (e.g., portions of the occipital lobe). Although the use of the Brunner-Munzel test with small samples sizes for an individual voxel has been criticized for elevated rates of Type 1 error (Medina, Kimberg, Chatterjee, & Coslett, 2010), significant results in the current study were in regions with sample sizes that exceeded the threshold of concern when using this test. While the current study utilized a traditional univariate approach to VLSM, a

multivariate approach that leverages the correlations among voxels to examine relationships may provide increased power for detecting associations (Zhang, Kimber, Coslett, Schwartz, & Wang, 2014).

There was a range in our sample of the duration between lesion onset and completion of the psychopathology measure. However, the majority of participants experienced the onset of their lesions in middle to late adulthood, a period of time with relative stability in levels of neuroticism (Roberts, Walton, & Viechtbauer, 2006), and repeated assessments in the chronic epoch of recovery have yielded stability in the association between lesion location and behavior (e.g., impairments in social and emotional functioning in patients with vmPFC damage: Damasio, Tranel, & Damasio, 1990; Barrash, Tranel, & Anderson, 2000; Robinson, Calamia, Gläscher, Bruss, Tranel, 2014). Although one strength of a lesion study is the ability to identify regions necessary for behavior, this technique does not address the dynamic associations of psychopathology and brain development over time. Finally, patients with severely impaired reading comprehension could not complete the MMPI and were not included in this study; however, this exclusion affected only a very small number of patients and thus was unlikely to have had a significant effect on the pattern of results (or external validity, at least in literate societies). Additionally, we included all patients (with relevant data) in all analyses rather than excluding based on scores on any validity scales. For only one validity scale, infrequent somatic complaints (Fs), was there a significant association with specific brain regions; this likely reflects genuine symptoms as several items on this scale, while rare in medical patients, overlap with symptoms common in those with epilepsy or other neurological disorders. A follow-up set of analyses (not shown) conducted after excluding patients with elevations on fixed or random responding scales (i.e., TRIN-r and VRIN-r: n=18) yielded a largely similar pattern of results for all but one scale; however, the number of significant voxels was smaller. Given that the overall pattern was similar, these differences in individual significant voxels may reflect decreased power with fewer patients. In addition, we had concerns about using these scales to exclude patients within our study given missing data and potential issues with imputation for scales whose interpretation is based on making a number of inconsistent responses across the entire measure. The use of imputation in general is a limitation of the current study. Finally, nearly all participants were Caucasian, which may limit the generalizability of the current findings.

4.4. Implications

The structure of psychopathology we found in our sample of patients with focal brain damage mirrors that found in psychiatric patient samples. The need to examine neural correlates of dimensions of psychopathology is being increasingly recognized (e.g., Zald & Lahey, 2017). The MMPI-2-RF is a broadband measure aligned with a recent proposal for examining hierarchical dimensions of psychopathology (Kotov et al., 2017) and the findings in the current study provide a foundation for future studies. Future studies administering the full MMPI-2-RF to patients with focal brain damage may be able to utilize additional scales (e.g., specific problem scales) to more comprehensively examine brain-behavior associations.

Lesion-symptom associations for various MMPI-2-RF scales were found in medial prefrontal cortex and areas of the temporal lobe, including medial temporal lobe structures such as the hippocampus and amygdala. Differences in the structure (e.g., reduced volume) and function (e.g., abnormal patterns of activation) within these regions have been found in neuroimaging studies of several different psychiatric disorders, likely reflecting the role of these regions in emotional processing (Phillips, Drevets, Rauch, & Lane, 2003). A recent meta-analysis of fMRI studies patients with mood, anxiety, and psychotic disorders found that, across disorders, several regions (including the amygdala and hippocampus) were associated with differences between patients and healthy comparison participants (Sprootenet al., 2017). In contrast, patterns of differences associated with a specific diagnosis were much less robust; this pattern supports the perspective of examining transdiagnostic factors of psychopathology.

Although there is considerable variability in findings within and across studies, research on the neural correlates of psychopathology using a diverse set of samples, from children followed longitudinally (e.g., Synder et al., 2017), to adults with psychiatric disorders (e.g., Bora et al., 2011), to older adults with dementia (e.g., Boublay et al., 2016) has often found associations between psychopathology and frontal and temporal regions, including regions identified in the current study (e.g., ventromedial prefrontal cortex, amygdala). Other research has emphasized the relationship of psychopathology to aberrant connectivity between frontal and temporal regions (e.g., Alnæs et al., 2018). These findings may reflect the relationship between psychopathology and dysfunctional emotional processing or cognition or their interaction (Beauchaine & Zisner, 2017; Cole, Repovš, & Anticevic, 2014). By using a lesion-based approach, the current study replicates and extends previous neuroimaging studies by identifying dysfunction in these regions as critical in the development of psychopathology. Research on the neural correlates of psychopathology may ultimately improve our understanding of who will respond to specific treatments and the neural mechanisms by which treatments work to yield clinical improvement (McKaya, & Tolin, In Press).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Abram SV, & DeYoung CG (2017). Using personality neuroscience to study personality disorder. Personality Disorders: Theory, Research, and Treatment, 8, 2–13.

Aldao A, Gee DG, De Los Reyes A, & Seager I (2016). Emotion regulation as a transdiagnostic factor in the development of internalizing and externalizing psychopathology: Current and future directions. Development and Psychopathology, 28, 927–946. [PubMed: 27739387]

Alfano DP, Finlayson MAJ, Stearns GM, & Neilson PM (1990). The MMPI and neurologic dysfunction: Profile configuration and analysis.The Clinical Neuropsychologist,4, 69–79. [PubMed: 29022433]

Allen TA, & DeYoung CG (2017 Personality neuroscience and the Five Factor Model In Widiger TA (Ed.), Oxford Handbook of the Five Factor Model. New York: Oxford University Press

Alnæs D, Kaufmann T, Doan NT, Córdova-Palomera A, Wang Y, Bettella F, … & Westlye LT (2018). Association of heritable cognitive ability and psychopathology with white matter properties in children and adolescents. JAMA psychiatry, 75, 287–295. [PubMed: 29365026]

Alves SG, Ferrer Carvalho A, de Amorim de Carvalho L, Kenji Sudo F, Ibiapina Siqueira-Neto J, Oertel-Knochel V, … & Pantel J (2017). Neuroimaging findings related to behavioral disturbances in Alzheimer's disease: a systematic review. Current Alzheimer Research, 14, 61–75. [PubMed: 27298146]

Andersen AL, & Hanvik LJ (1950). The psychometric localization of brain lesions: The differential effect of frontal and parietal lesions on MMPI profiles. Journal of Clinical Psychology, 6, 177–180.

Anderson JL, Sellbom M, Bagby RM, Quilty LC, Veltri CO, Markon KE, & Krueger RF (2013). On the convergence between PSY-5 domains and PID-5 domains and facets implications for assessment of DSM-5 personality traits. Assessment, 20, 286–294. [PubMed: 23297369]

Andreasen NC (1988). Brain imaging: applications in psychiatry. Science, 239, 1381–1388. [PubMed: 3279509]

Barrash J, Tranel D, & Anderson SW (2000). Acquired personality disturbances associated with bilateral damage to the ventromedial prefrontal region. Developmental Neuropsychology, 18, 355–381. [PubMed: 11385830]

Bates E, Wilson SM, Saygin AP, Dick F, Sereno MI, Knight RT, & Dronkers NF (2003). Voxel-based lesion–symptom mapping. Nature Neuroscience, 6, 448–450. [PubMed: 12704393]

Beauchaine TP, & Zisner A (2017). Motivation, emotion regulation, and the latent structure of psychopathology: an integrative and convergent historical perspective. International Journal of Psychophysiology, 119, 108–118. [PubMed: 28057475]

Ben-Porath YS (2012). Interpreting the MMPI-2-RF. Minneapolis, MN: University of Minnesota Press.

Ben-Porath YS, & Tellegen A (2008). Minnesota Multiphasic Personality Inventory-2-Restructured Form (MMPI-2-RF): Manual for administration, scoring, and interpretation. Minneapolis, MN: University of Minnesota Press.

Benton AL, Hamsher K. de S., Rey GJ, & Sivan AB (1994). Multilingual Aphasia Examination (3rd ed.). Iowa City, IA: AJA Associates.

Boes AD, Prasad S, Liu H, Liu Q, Pascual-Leone A, Caviness VS Jr, & Fox MD (2015). Network localization of neurological symptoms from focal brain lesions. Brain, 138, 3061–3075. [PubMed: 26264514]

Bogousslavsky J, Van Melle G, & Regli F (1988). The Lausanne Stroke Registry: analysis of 1,000 consecutive patients with first stroke. Stroke, 19, 1083–1092. [PubMed: 3413804]

Bora E, Fornito A, Pantelis C, & Yücel M (2012). Gray matter abnormalities in major depressive disorder: a meta-analysis of voxel based morphometry studies. Journal of Affective Disorders, 138, 9–18. [PubMed: 21511342]

Bora E, Fornito A, Radua J, Walterfang M, Seal M, Wood SJ, … & Pantelis C (2011). Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis.Schizophrenia research,127, 46–57. [PubMed: 21300524]

Boublay N, Schott AM, & Krolak-Salmon P (2016). Neuroimaging correlates of neuropsychiatric symptoms in Alzheimer's disease: a review of 20 years of research. European Journal of Neurology, 23, 1500–1509. doi: 10.1111/ene.13076 [PubMed: 27435186]

Brunner E, & Munzel U (2000). The Nonparametric Behrens-Fisher Problem: Asymptotic Theory and a Small-Sample Approximation. Biometrical Journal, 42, 17–25.

Camara WJ, Nathan JS, & Puente AE (2000). Psychological test usage: Implications in professional psychology. Professional Psychology: Research and Practice, 31, 141–154.

Cole MW, Repovš G, & Anticevic A (2014). The frontoparietal control system: a central role in mental health. The Neuroscientist, 20, 652–664. [PubMed: 24622818]

Damasio AR, Tranel D, & Damasio H (1990). Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. Behavioural Brain Research, 41, 81–94. [PubMed: 2288668]

Dannlowski U, Stuhrmann A, Beutelmann V, Zwanzger P, Lenzen T, Grotegerd D, … & Lindner C (2012). Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. Biological Psychiatry, 71, 286–293. [PubMed: 22112927]

de Oliveira-Souza R, Hare RD, Bramati IE, Garrido GJ, Ignácio FA, Tovar-Moll F, & Moll J (2008). Psychopathy as a disorder of the moral brain: fronto-temporo-limbic grey matter reductions demonstrated by voxel-based morphometry. Neuroimage, 40, 1202–1213. [PubMed: 18289882]

DeYoung CG, Hirsh JB, Shane MS, Papademetris X, Rajeevan N, & Gray JR (2010). Testing predictions from personality neuroscience brain structure and the big five. Psychological Science, 21, 820–828. [PubMed: 20435951]

Dikmen S, & Reitan RM (1977). Emotional sequelae of head injury. Annals of Neurology, 2, 492–494. [PubMed: 617591]

Ermer E, Cope LM, Nyalakanti PK, Calhoun VD, & Kiehl KA (2012). Aberrant paralimbic gray matter in criminal psychopathy. Journal of Abnormal Psychology, 121, 649–658. [PubMed: 22149911]

Ersche KD, Williams GB, Robbins TW, & Bullmore ET (2013). Meta-analysis of structural brain abnormalities associated with stimulant drug dependence and neuroimaging of addiction vulnerability and resilience. Current Opinion in Neurobiology, 23, 615–624. [PubMed: 23523373]

Fiez JA, Damasio H, & Grabowski TJ (2000). Lesion segmentation and manual warping to a reference brain: intra-and interobserver reliability. Human Brain Mapping, 9, 192–211. [PubMed: 10770229]

Frank RJ, Damasio H, & Grabowski TJ (1997). Brainvox: an interactive, multimodal visualization and analysis system for neuroanatomical imaging. Neuroimage, 5, 13–30. [PubMed: 9038281]

Frank DW, Dewitt M, Hudgens-Haney M, Schaeffer DJ, Ball BH, Schwarz NF, … & Sabatinelli D (2014). Emotion regulation: quantitative meta-analysis of functional activation and deactivation. Neuroscience & Biobehavioral Reviews, 45, 202–211. [PubMed: 24984244]

Fried EI, & Nesse RM (2015). Depression is not a consistent syndrome: an investigation of unique symptom patterns in the STAR* D study. Journal of Affective Disorders, 172, 96–102. [PubMed: 25451401]

Fried EI, Nesse RM, Zivin K, Guille C, & Sen S (2014). Depression is more than the sum score of its parts: individual DSM symptoms have different risk factors. Psychological Medicine, 44, 2067–2076. [PubMed: 24289852]

Fusar-Poli P, Radua J, Frascarelli M, Mechelli A, Borgwardt S, Fabio F, … & David SP (2014). Evidence of reporting biases in voxel-based morphometry (VBM) studies of psychiatric and neurological disorders. Human Brain Mapping, 35, 3052–3065. [PubMed: 24123491]

Gass CS (1992). MMPI-2 interpretation of patients with cerebrovascular disease: A correction factor. Archives of Clinical Neuropsychology, 7, 17–27. [PubMed: 14589675]

Godsil BP, Kiss JP, Spedding M, & Jay TM (2013). The hippocampal–prefrontal pathway: The weak link in psychiatric disorders?. European Neuropsychopharmacology, 23, 1165–1181. [PubMed: 23332457]

Gläscher J, Tranel D, Paul LK, Rudrauf D, Rorden C, Hornaday A, … & Adolphs R (2009). Lesion mapping of cognitive abilities linked to intelligence. Neuron, 61, 681–691. [PubMed: 19285465]

Glorfeld LW (1995). An improvement on Horn's parallel analysis methodology for selecting the correct number of factors to retain. Educational & Psychological Measurement, 55, 377–393.

Goodkind M, Eickhoff SB, Oathes DJ, Jiang Y, Chang A, Jones-Hagata LB, … & Grieve SM (2015). Identification of a common neurobiological substrate for mental illness. JAMA Psychiatry, 72, 305–315. [PubMed: 25651064]

Gur RE, Skolnick BE, Gur RC, Caroff S, Rieger W, Obrist WD, … & Reivich M (1984). Brain function in psychiatric disorders: II. Regional cerebral blood flow in medicated unipolar depressives. Archives of General Psychiatry, 41, 695–699. [PubMed: 6732427]

Haas BW, Ishak A, Anderson IW, & Filkowski MM (2015). The tendency to trust is reflected in human brain structure. NeuroImage, 107, 175–181. [PubMed: 25485710]

Hägele C, Friedel E, Schlagenhauf F, Sterzer P, Beck A, Bermpohl F, … & Heinz A (2016). Affective responses across psychiatric disorders—A dimensional approach. Neuroscience Letters, 623, 71–78. [PubMed: 27130821]

Harkness AR, McNulty JL, Finn JA, Reynolds SM, Shields SM, & Arbisi P (2014). The MMPI–2–RF Personality Psychopathology Five (PSY–5–RF) Scales: Development and validity research. Journal of Personality Assessment, 96, 140–150. [PubMed: 23941166]

Hoelzle JB, & Meyer GJ (2008). The factor structure of the MMPI-2 Restructured Clinical (RC) scales. Journal of Personality Assessment, 90, 443–455. [PubMed: 18704803]

Hu LT, & Bentler PM (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Structural Equation Modeling: A Multidisciplinary Journal, 6, 1–55.

Huey ED, Lee S, Lieberman JA, Devanand DP, Brickman AM, Raymont V, … & Grafman J (2015). Brain regions associated with internalizing and externalizing psychiatric symptoms in patients with penetrating traumatic brain injury. The Journal of Neuropsychiatry and Clinical Neurosciences, 28, 104–111. [PubMed: 26715034]

Kalin NH, & Shelton SE (2003). Nonhuman primate models to study anxiety, emotion regulation, and psychopathology. Annals of the New York Academy of Sciences, 1008, 189–200. [PubMed: 14998885]

Karl A, Schaefer M, Malta LS, Dörfel D, Rohleder N, & Werner A (2006). A meta-analysis of structural brain abnormalities in PTSD. Neuroscience & Biobehavioral Reviews, 30, 1004–1031. [PubMed: 16730374]

Knutson KM, Monte OD, Raymont V, Wassermann EM, Krueger F, & Grafman J (2014). Neural correlates of apathy revealed by lesion mapping in participants with traumatic brain injuries. Human Brain Mapping, 35, 943–953. [PubMed: 23404730]

Koenigs M, Huey ED, Calamia M, Raymont V, Tranel D, & Grafman J (2008). Distinct regions of prefrontal cortex mediate resistance and vulnerability to depression. The Journal of Neuroscience, 28, 12341–12348. [PubMed: 19020027]

Koscik T, & Tranel D (2012). Brain evolution and human neuropsychology: The Inferential Brain Hypothesis. Journal of the International Neuropsychological Society, 18, 394–401. [PubMed: 22459075]

Kotov R, Gamez W, Schmidt F, & Watson D (2010). Linking “big” personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. Psychological Bulletin, 136, 768–821. [PubMed: 20804236]

Kotov R, Krueger RF, Watson D, Achenbach TM, Althoff RR, Bagby RM.. Zimmerman M (2017). The Hierarchical Taxonomy of Psychopathology (HiTOP): A Dimensional Alternative to Traditional Nosologies Journal of Abnormal Psychology. Advance online publication.

Kozak MJ, & Cuthbert BN (2016). The NIMH research domain criteria initiative: Background, issues, and pragmatics. Psychophysiology, 53, 286–297. [PubMed: 26877115]

Krajbich I, Adolphs R, Tranel D, Denburg NL, & Camerer CF (2009). Economic games quantify diminished sense of guilt in patients with damage to the prefrontal cortex. The Journal of Neuroscience, 29, 2188–2192. [PubMed: 19228971]

Krueger RF, & DeYoung CG (2016). The RDoC initiative and the structure of psychopathology. Psychophysiology, 53, 351–354. [PubMed: 26877125]

Krueger RF, & Markon KE (2006). Reinterpreting comorbidity: A model-based approach to understanding and classifying psychopathology. Annual Review of Clinical Psychology, 2, 111–133.

Krueger RF, Markon KE, Patrick CJ, Benning SD, & Kramer MD (2007). Linking antisocial behavior, substance use, and personality: an integrative quantitative model of the adult externalizing spectrum. Journal of Abnormal Psychology, 116, 645–666. [PubMed: 18020714]

Kühn S, & Gallinat J (2013). Gray matter correlates of posttraumatic stress disorder: a quantitative meta-analysis. Biological Psychiatry, 73, 70–74. [PubMed: 22840760]

Lang PJ, Davis M, & Öhman A (2000). Fear and anxiety: animal models and human cognitive psychophysiology. Journal of Affective Disorders, 61, 137–159. [PubMed: 11163418]

Lewis PA, Rezaie R, Brown R, Roberts N, & Dunbar RI (2011). Ventromedial prefrontal volume predicts understanding of others and social network size. Neuroimage, 57, 1624–1629. [PubMed: 21616156]

Levenson RW, Sturm VE, & Haase CM (2014). Emotional and behavioral symptoms in neurodegenerative disease: a model for studying the neural bases of psychopathology. Annual Review of Clinical Psychology, 10, 581–606.

Lilienfeld S, Reber J, Hamann S, Watts AL, Sauvigne K, Murphy B, …Tranel D (2016). Potential effects of bilateral amygdala damage on psychopathic personality features: A case report Personality Disorders: Theory, Research, and Treatment. Advance online publication.

Mah YH, Husain M, Rees G, & Nachev P (2014). Human brain lesion-deficit inference remapped. Brain, 137, 2522–2531. [PubMed: 24974384]

Markon KE, Chmielewski M, & Miller CJ (2011). The reliability and validity of discrete and continuous measures of psychopathology: a quantitative review. Psychological Bulletin, 137, 856–879. [PubMed: 21574681]

Marusak HA, Thomason ME, Peters C, Zundel C, Elrahal F, & Rabinak CA (2016). You say 'prefrontal cortex'and I say 'anterior cingulate': meta-analysis of spatial overlap in amygdala-to-prefrontal connectivity and internalizing symptomology. Translational Rsychiatry, 6, e944.

Mathew I, Gardin TM, Tandon N, Eack S, Francis AN, Seidman LJ, … & Keshavan MS (2014). Medial temporal lobe structures and hippocampal subfields in psychotic disorders: findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. JAMA Psychiatry, 71, 769–777. [PubMed: 24828364]

Matsuo K, Nicoletti M, Nemoto K, Hatch JP, Peluso MA, Nery FG, & Soares JC (2009). A voxel-based morphometry study of frontal gray matter correlates of impulsivity. Human Brain Mapping, 30, 1188–1195. [PubMed: 18465751]

McKay D, & Tolin DF (2016). Empirically supported psychological treatments and the Research Domain Criteria (RDoC). Journal of Affective Disorders. Advanced Online Publication.

McTeague LM, Huemer J, Carreon DM, Jiang Y, Eickhoff SB, & Etkin A (2017). Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. American Journal of Psychiatry, 174, 676–685. [PubMed: 28320224]

Medina J, Kimberg DY, Chatterjee A, & Coslett HB (2010). Inappropriate usage of the Brunner–Munzel test in recent voxel-based lesion-symptom mapping studies. Neuropsychologia, 48, 341–343. [PubMed: 19766664]

Mihura JL, Roy M, & Graceffo RA (2016). Psychological Assessment Training in Clinical Psychology Doctoral Programs Journal of Personality Assessment. Advance online publication.

Milaneschi Y, Lamers F, Peyrot WJ, Abdellaoui A, Willemsen G, Hottenga JJ, … & Boomsma DI (2016). Polygenic dissection of major depression clinical heterogeneity. Molecular Psychiatry, 21, 516–522. [PubMed: 26122587]

Mincic AM (2015). Neuroanatomical correlates of negative emotionality-related traits: A systematic review and meta-analysis. Neuropsychologia, 77, 97–118. [PubMed: 26265397]

Morgane PJ, Galler JR, & Mokler DJ (2005). A review of systems and networks of the limbic forebrain/limbic midbrain. Progress in Neurobiology, 75, 143–160. [PubMed: 15784304]

Nikolas M, Markon K, & Tranel D (2016). Psychopathology: Neurobiological and genetic mechanisms In Maddux JE & Winstead BA (Eds.). Psychopathology: Foundations for a Contemporary Understanding (4th ed., pp. 27–58). New York: Routledge/Taylor & Francis.

O'Connor BP (2002). The search for dimensional structure differences between normality and abnormality: A statistical review of published data on personality and psychopathology. Journal of Personality and Social Psychology, 83, 962–982. [PubMed: 12374447]

Oler JA, Fox AS, Shelton SE, Rogers J, Dyer TD, Davidson RJ, … & Kalin NH (2010). Amygdalar and hippocampal substrates of anxious temperament differ in their heritability. Nature, 466, 864–868. [PubMed: 20703306]

Olson IR, Plotzker A, & Ezzyat Y (2007). The enigmatic temporal pole: a review of findings on social and emotional processing. Brain, 130, 1718–1731. [PubMed: 17392317]

Phillips ML, Drevets WC, Rauch SL, & Lane R (2003). Neurobiology of emotion perception II: Implications for major psychiatric disorders. Biological Psychiatry, 54, 515–528. [PubMed: 12946880]

Poldrack RA, & Farah MJ (2015). Progress and challenges in probing the human brain. Nature, 526, 371–379. [PubMed: 26469048]

Post RM (2000). Neural substrates of psychiatric syndromes In Mesulam MM (Ed.), Principles of Behavioral and Cognitive Neurology. (2nd Ed.) (pp.406–438). New York: Oxford University Press.

Pustina D, Avants B, Faseyitan OK, Medaglia JD, & Coslett HB (2017). Improved accuracy of lesion to symptom mapping with multivariate sparse canonical correlations Neuropsychologia. Advance online publication. doi: 10.1016/j.neuropsychologia.2017.08.027

Qi C, Roseboom PH, Nanda SA, Lane JC, Speers JM, & Kalin NH (2010). Anxiety-related behavioral inhibition in rats: a model to examine mechanisms underlying the risk to develop stress-related psychopathology. Genes, Brain and Behavior, 9, 974–984.

Rabin LA, Paolillo E, & Barr WB (2016). Stability in test-usage practices of clinical neuropsychologists in the United States and Canada over a 10-year period: A follow-up survey of INS and NAN members. Archives of Clinical Neuropsychology, 31, 206–230. [PubMed: 26984127]

Riccelli R, Toschi N, Nigro S, Terracciano A, & Passamonti L (2017). Surface-based morphometry reveals the neuroanatomical basis of the five-factor model of personality. Social Cognitive and Affective Neuroscience, 12, 671–684. [PubMed: 28122961]

Roberts BW, Walton KE, & Viechtbauer W (2006). Patterns of mean-level change in personality traits across the life course: a meta-analysis of longitudinal studies. Psychological Bulletin, 132, 1–25. [PubMed: 16435954]

Robinson H, Calamia M, Gläscher J, Bruss J, & Tranel D (2014). Neuroanatomical correlates of executive functions: a neuropsychological approach using the EXAMINER battery. Journal of the International Neuropsychological Society, 20, 52–63. [PubMed: 23759126]

Rorden C, & Karnath HO (2004). Using human brain lesions to infer function: a relic from a past era in the fMRI age?. Nature Reviews Neuroscience, 5, 812–819.

Rorden C, Karnath HO, & Bonilha L (2007). Improving lesion-symptom mapping. Journal of Cognitive Neuroscience, 19,1081–1088. [PubMed: 17583985]

Sellbom M, Ben-Porath YS, & Bagby RM (2008). Personality and psychopathology: Mapping the MMPI-2 Restructured Clinical (RC) Scales onto the five factor model of personality. Journal of Personality Disorders, 22, 291–312. [PubMed: 18540801]

Servaas MN, Van Der Velde J, Costafreda SG, Horton P, Ormel J, Riese H, & Aleman A (2013). Neuroticism and the brain: a quantitative meta-analysis of neuroimaging studies investigating emotion processing. Neuroscience & Biobehavioral Reviews, 37, 1518–1529. [PubMed: 23685122]

Simms LJ, Casillas A, Clark LA, Watson D, & Doebbeling BN (2005). Psychometric evaluation of the restructured clinical scales of the MMPI-2. Psychological Assessment, 17, 345–358. [PubMed: 16262460]

Snyder HR, Hankin BL, Sandman CA, Head K, & Davis EP (2017). Distinct patterns of reduced prefrontal and limbic gray matter volume in childhood general and internalizing psychopathology. Clinical Psychological Science, 5, 1001–1013. [PubMed: 29399423]

Sprooten E, Rasgon A, Goodman M, Carlin A, Leibu E, Lee WH, & Frangou S (2017). Addressing reverse inference in psychiatric neuroimaging: Meta-analyses of task-related brain activation in common mental disorders Human Brain Mapping. Advance online publication.

Sundram F, Cannon M, Doherty CP, Barker GJ, Fitzsimons M, Delanty N, & Cotter D (2010). Neuroanatomical correlates of psychosis in temporal lobe epilepsy: voxel-based morphometry study. The British Journal of Psychiatry, 197, 482–492. [PubMed: 21119155]

Sutterer MJ, Bruss J, Boes AD, Voss MW, Bechara A, & Tranel D (2016). Canceled connections: Lesion-derived network mapping helps explain differences in performance on a complex decision-making task. Cortex, 78, 31–43. [PubMed: 26994344]

Tarescavage AM, Corey DM, & Ben-Porath YS (2016). A Prorating Method for Estimating MMPI-2-RF Scores From MMPI Responses Examination of Score Fidelity and Illustration of Empirical

Utility in the PERSEREC Police Integrity Study Sample. Assessment, 23, 173–190. [PubMed: 25848124]

Tellegen A, & Ben-Porath YS (2008). MMPI-2-RF, Minnesota Multiphasic Personality Inventory-2 Restructured Form: Technical Manual. University of Minnesota Press.

van Tol MJ, van der Wee NJ, van den Heuvel OA, Nielen MM, Demenescu LR, Aleman A, … & Veltman DJ (2010). Regional brain volume in depression and anxiety disorders. Archives of General Psychiatry, 67, 1002–1011. [PubMed: 20921116]

Weinberger DR, & Radulescu E (2015). Finding the elusive psychiatric “lesion” with 21st-century neuroanatomy: a note of caution. American Journal of Psychiatry, 173, 27–33. [PubMed: 26315983]

Whitehead D, Tunnard C, Hurt C, Wahlund LO, Mecocci P, Tsolaki M, … & Simmons A (2012). Frontotemporal atrophy associated with paranoid delusions in women with Alzheimer’s disease. International Psychogeriatrics, 24, 99–107. [PubMed: 21740613]

Whittle S, Allen NB, Lubman DI, & Yücel M (2006). The neurobiological basis of temperament: towards a better understanding of psychopathology. Neuroscience & Biobehavioral Reviews, 30, 511–525. [PubMed: 16289282]

Wilkinson GS, & Robertson GJ (2006). WRAT4: Wide Range Achievement Test Professional Manual. Lutz, FL: Psychological Assessment Resources, Inc.

Wolf AW, Schubert DS, Patterson MB, Grande TP, Brocco KJ, & Pendleton L (1988). Associations among major psychiatric diagnoses. Journal of Consulting and Clinical Psychology, 56, 292–294. [PubMed: 3372837]

Wright AG, Krueger RF, Hobbs MJ, Markon KE, Eaton NR, & Slade T (2013). The structure of psychopathology: toward an expanded quantitative empirical model. Journal of Abnormal Psychology, 122, 281–294. [PubMed: 23067258]

Xia CH, Ma Z, Ciric R, Gu S, Betzel RF, Kaczkurkin AN, … & Moore TM (2017). Linked dimensions of psychopathology and connectivity in functional brain networks. bioRxiv. doi: 10.1101/199406

Yang Y, & Raine A (2009). Prefrontal structural and functional brain imaging findings in antisocial, violent, and psychopathic individuals: a meta-analysis. Psychiatry Research: Neuroimaging, 174, 81–88.

Yarknoi T (2015). Neural Substrates of Personality: A Critical Review. In Mikulincer M & Shaver PR (Eds.), APA Handbook of Personality and Social Psychology: Vol. 4 Personality Processes and Individual Differences (pp. 61–83). Washington, DC: American Psychological Association.

Zald DH, & Lahey BB (2017). Implications of the hierarchical structure of psychopathology for psychiatric neuroimaging. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 2, 310–317. [PubMed: 28713866]

Zhang Y, Kimberg DY, Coslett HB, Schwartz MF, & Wang Z (2014). Multivariate lesion-symptom mapping using support vector regression.Human Brain Mapping,35, 5861–5876. doi: 10.1002/hbm.22590 [PubMed: 25044213]

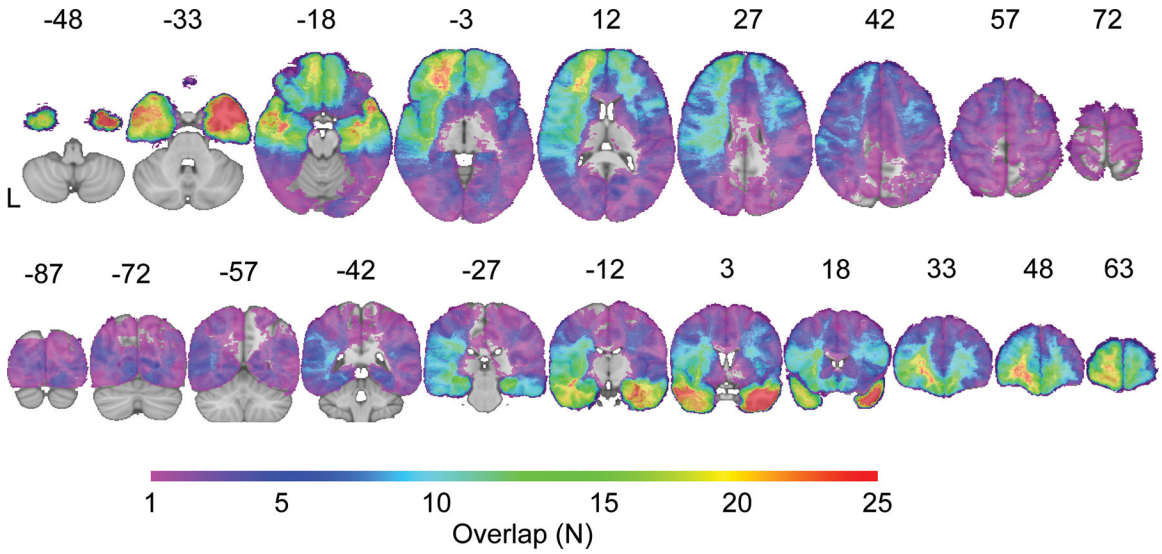

Figure 1:

Lesion overlap map. Lesion overlap in MNI standard space of study participants. Top row coordinates are MNI space z-coordinates of axial slices, while bottom row coordinates are MNI space y-coordinates. Images are in neurological convention (left hemisphere is on the left side of the image).

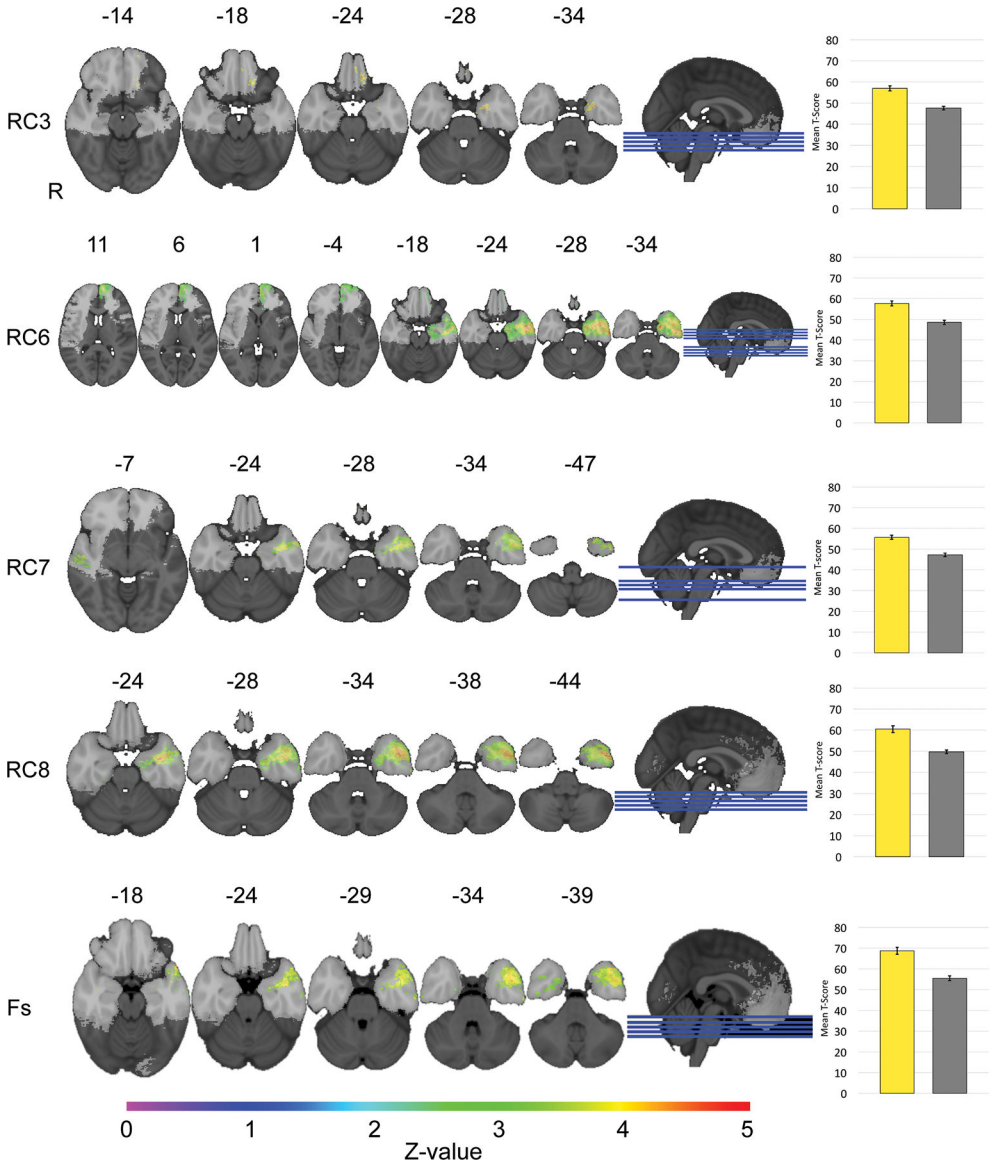

Figure 2:

Descending axial sections (each row: most superior slice on left to most inferior slice on right, MNI space z-coordinates shown above) showing areas of significant (FDR-corrected $p < 0.05$) voxel-lesion symptom mapping for MMPI-2-RF restructured clinical (RC3,6,7 and 8) and validity scales (Fs). Higher z-value reflects stronger association between damage to that area and elevated score, brain regions shaded in dark gray lack sufficient power to detect an effect. Brain slices are shown in radiological convention (i.e., left hemisphere is on the right side of the image). Bar graphs show mean (±SEM) score for patients with damage falling within the significant regions (yellow), compared to patients with damage falling outside that area (gray). RC3 = Cynicism; RC6 = Ideas of Persecution (i.e., self-referential beliefs of persecution), RC7 = Dysfunctional Negative Emotions (e.g., experiences of anxiety, fear, and anger), RC8 = Aberrant Experiences (i.e., atypical thought and sensory

experiences); Fs = Infrequent Somatic Responses (i.e., atypical somatic complaints relative to those with genuine medical problems).

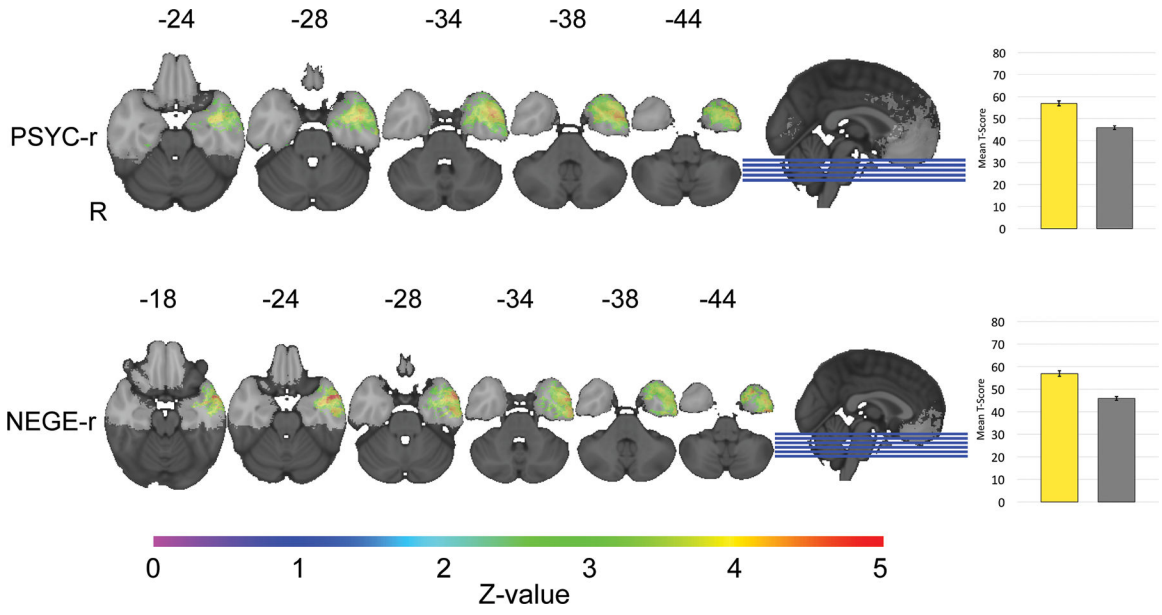

Figure 3:

Descending MNI space axial sections showing areas of significant (FDR-corrected $p < 0.05$) voxel-lesion symptom mapping for MMPI-2-RF Personality Psychopathology Five Revised (PSY-5-RF) scales (PSYC-r and NEGE-r). Higher z-value reflects stronger association between damage to that area and elevated score, brain regions shaded in dark gray lack sufficient power to detect an effect. Bar graphs at right show mean (±SEM) score for patients with damage falling within the significant regions (yellow), compared to patients with damage falling outside that area (gray). PSYC-r = Psychoticism-Revised (e.g., atypical thought and sensory experiences; alienation from others); NEGE-r = Negative Emotionality/ Neuroticism-Revised (e.g., tendency to experience anxiety, worry, and other negative emotions).

Table 1.

Results from Voxel-Based Lesion-Symptom Analyses Showing Regions of Damage Associated with Increased MMPI-2-RF Restructured Clinical and Validity Scale Scores.

Scale	Region(s)	x	y	z	Z-score	Cluster Size
RC3	L Temporal Pole, Anterior Parahippocampal Gyrus, Amygdala	−28	2	−40	4.66	1,148
	L Frontal Orbital Cortex, Frontal Pole	−10	35	−25	4.91	662
	L Frontal Pole	−10	66	16	4.17	193
	L Frontal Medial Cortex	−2	45	−27	3.89	137
	L Frontal Pole	−4	64	24	3.89	105
RC6	L Posterior Middle Temporal Gyrus, Temporal Pole, Inferior Temporal Gyrus, Parahippocampal Gyrus, Hippocampus, Amygdala, Temporal Fusiform Cortex	−63	−11	−30	5.11	36,114
	L Frontal Pole, Paracingulate Gyrus	−5	61	−4	4.12	14,504
RC7	L Anterior Middle Temporal Gyrus, Temporal Pole, Anterior Parahippocampal Gyrus, Temporal Fusiform Cortex	−58	2	−33	4.43	10,264
	R Posterior Superior Temporal Gyrus, Posterior Middle Temporal Gyrus	53	−14	−5	3.86	903
RC8	L Temporal Pole, Temporal Fusiform Cortex, Anterior Parahippocampal Gyrus, Amygdala, Hippocampus	−44	9	−45	4.81	16,465
Fs	L Temporal Pole, Hippocampus, Temporal Fusiform Cortex, Inferior Temporal Gyrus	−56	15	−13	5.05	12,173
	R anterior parahippocampal gyrus, Temporal fusiform cortex	21	−7	−34	3.66	1,847
	L inferior temporal gyrus, Posterior middle temporal gyrus	−60	−16	−35	4.03	348

Note: L refers to the left hemisphere and R to the right hemisphere. Cluster maps thresholded at the FDR corrected $p < 0.05$ level for each scale. Coordinates are in MNI space. Cluster size is in voxels. Regions defined using the Harvard-Oxford probabilistic cortical and subcortical atlases in FSL.

Table 2.

Results from Voxel-Based Lesion-Symptom Analyses Showing Regions of Damage Associated with Increased MMPI-2-RF Personality-Psychopathology-5-Revised Scale Scores.

Scale	Region(s)	x	y	z	Z-score	Cluster Size
PSYC-r	L Temporal Pole, Anterior Inferior Temporal Gyrus	−28	6	−48	4.67	20,793
	R Posterior Middle Temporal Gyrus, Posterior Superior Temporal Gyrus	69	−18	−7	4.00	989
NEGE-r	L Temporal Pole, Anterior Parahippocampal Gyrus, Temporal Fusiform Cortex, Hippocampus, Amygdala	−54	4	−24	5.47	22,933
	L Paracingulate Gyrus, Superior Frontal Gyrus	−10	30	34	3.22	1,592

Note: L refers to the left hemisphere and R to the right hemisphere. Cluster maps thresholded at the FDR corrected $p < 0.05$ level for each scale. Coordinates are in MNI space. Cluster size is in voxels. Regions defined using the Harvard-Oxford probabilistic cortical and subcortical atlases in FSL.