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Published on: 31 Jan 2020 - bioRxiv (Cold Spring Harbor Laboratory)

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TITLE

Common default mode network dysfunction across psychopathologies: A neuroimaging meta-analysis of the n-back working memory paradigm

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ABSTRACT

The National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC) classifies disorders based on shared aspects of behavioral and neurobiological dysfunction. One common behavioral deficit observed in various psychopathologies, namely ADHD, addiction, bipolar disorder, depression, and schizophrenia, is a deficit in working memory performance. However, it is not known to what extent, if any, these disorders share common neurobiological abnormalities that contribute to decrements in performance. The goal of the present study was to examine convergence and divergence of working memory networks across psychopathologies. We used the Activation Likelihood Estimate (ALE) meta-analytic technique to collapse prior data obtained from published studies using the n-back working memory paradigm in individuals with a DSM-criteria diagnosis of the aforementioned disorders. These studies examined areas in the brain that showed increases in activity as a function of working memory-related load compared to a baseline condition, both within subjects and between healthy individuals and those with psychiatric disorder. A meta-analysis of 281 foci covering 81 experiments and 2,629 participants found significant convergence of hyperactivity in medial prefrontal cortex (mPFC) for DSM-diagnosed individuals compared to healthy controls. Foci from ADHD, addiction, bipolar disorder, schizophrenia, and major depression studies contributed to the formation of this cluster. These results provide evidence that default-mode intrusion may constitute a shared seed of dysregulation across multiple psychopathologies, ultimately resulting in poorer working memory performance. (WORD COUNT: 224)

Keywords: n-back task, meta-analysis, working memory, psychopathology, ADHD, addiction, depression, bipolar disorder, schizophrenia

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INTRODUCTION

Deficits in working memory performance are a shared feature across many psychopathologies: depression (1), attention-deficit hyperactivity disorder (ADHD) (2), schizophrenia (3,4), addiction (5), and bipolar disorder (6). The extent to which the observed impairments are the result of similar neurobiological abnormalities has not been systematically explored. Understanding the shared as well as the unique neurobiological mechanisms that are related to poor working memory performance in different psychopathologies may impact understanding of their pathophysiology, as well as inform the diagnosis and treatment of these diseases. Moreover, this approach seeks to bridge the gap between clinically-derived classification schemes and cognitive neuroscience research outlined by the National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC) initiative (7). To our knowledge, no attempts have been made to reconcile the varied functional neuroimaging data that have emerged from research examining working memory across psychopathologies. Patients with schizophrenia, for example, have been shown to exhibit both hypoactivity and hyperactivity in left middle frontal gyrus in response to increased working memory load on the n-back task (3,8). Similarly, in Major Depressive Disorder (MDD), studies have reported decreases in insula activity during n-back performance (9) while others have reported the opposite effect (10).

To make sense of these disparate results, meta-analytic techniques such as the Activation Likelihood Estimation (ALE) algorithm can be implemented (11,12). The ALE algorithm provides a statistically rigorous approach to aggregating neuroimaging data that allows researchers to draw inferences using whole-brain peak coordinates (13,14). The ALE method, aggregating over studies, can be used to determine the likelihood a region contributes to a given contrast of interest (12). This is particularly valuable due to the drawbacks of individual

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88 neuroimaging studies, namely low statistical power, high false positive rates, and potential for
89 software errors (15).

90 The goal of the present study was to examine the convergence and/or divergence of
91 functional neuroimaging findings as it relates to working memory-related load across
92 psychopathologies, namely, ADHD, schizophrenia, addiction, depression, and bipolar disorder.
93 We chose to examine working memory-related load across various permutations of the n-back
94 task, which has been extensively validated as a probe for our psychological construct of interest
95 (16). First, we aggregated all peer-reviewed publications meeting our search criteria. All papers
96 had to include contrasts with patients having a DSM diagnosis of interest. Exceptions were made
97 for the 'Addiction' contrast to include illicit substance use more broadly, due to the lack of a
98 pervasive application of DSM criteria in this case. Imaging analyses furthermore had to include a
99 *minimum* n-back contrast of 2-back > rest. That is, a 2-back (or 3-back) > rest contrast was
100 acceptable for our purposes, but not 1-back > rest, 1-back > 0-back, or 3-back with no baseline.
101 Second, we extracted coordinates from all articles reporting within-group contrasts as well as
102 between-group contrasts (e.g., controls > bipolar disorder). Third, we ran each contrast in the
103 GingerALE software to create thresholded ALE images. We examined convergence within
104 psychopathologies to characterize the working memory-related activation patterns specific to
105 each disease. We then examined convergence between psychopathologies to identify regions that
106 showed either shared or unique contributions to the neurobiological differences related to
107 working memory performance.

108 Differences between psychopathology and control group activation maps may constitute
109 regions that warrant further investigation. Any focus of hyperactivation or hypoactivation across
110 psychopathologies compared to controls may represent functional biomarkers of pathology. In

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111 particular, these regions (or region) may play a pivotal role in the pathophysiology of working-
112 memory related deficits commonly observed in ADHD, addiction, bipolar disorder, depression
113 and schizophrenia. Such a finding may suggest a novel target for treatment, a potential new way
114 to predict the onset of mental illness, or a functional consequence resulting from the
115 development of psychiatric illness.
116
117 **METHODS**
118 **Criteria Selection for Data Used for Meta-Analysis**. We conducted literature
119 searches in both Google Scholar and PubMed utilizing the following terms alone and in
120 combination: 'n-back,' 'working memory,' '2-back,' and '3-back'. We constrained our results by
121 keywords related to our psychopathologies of interest: 'addiction,' 'nicotine,' 'cocaine,'
122 'marijuana,' 'ecstasy,' 'MDMA,' 'schizophrenia,' 'schizoaffective,' 'MDD,' 'depression,'
123 'bipolar,' 'mania,' and 'ADHD.' Peer reviewed articles were also obtained using BrainMap's
124 Sleuth 3.0.3 software (17) employing the search procedure: Experiments → Paradigm Class →
125 n-back and Subjects → Diagnosis → Alcoholism, Attention Deficit/ Hyperactivity Disorder,
126 Bipolar Disorder, Depression, Major Depressive Disorder, Schizophrenia, and Substance Use
127 Disorder. The obtained papers were further searched for citations of interest and authors were
128 contacted directly if peak coordinates were missing from their reported analyses.
129 Studies were grouped into separate diagnostic categories determined by DSM-criteria at
130 the time of their publication. This procedure resulted in the following five categories: Addiction,
131 ADHD, Bipolar Disorder, MDD, and Schizophrenia. We used the DSM-V diagnostic criteria for
132 classification purposes if a disorder was ambiguous. For example, Schizoaffective disorder was
133 classified within the "Schizophrenia" category, as it fits within the DSM-V's diagnostic category

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of "Schizophrenia Spectrum and Other Psychotic Disorders." We included subjects with illicit substance use in the 'Addiction' contrast even if they did not have a DSM criteria diagnosis.

We only included experiments using variants (e.g., phonological, visuospatial, emotional) of the n-back paradigm (16) in our meta-analysis. Acceptable experimental conditions included 3-back and 2-back paradigms, while 1-back, 0-back, fixation, and resting conditions were considered acceptable baselines. Preferred baseline conditions were 1-back and 0-back conditions, as subtraction of these conditions allows for removal of common sensory-motor effects associated with subjects' responses via button press (18). In rare cases, however, fixation or rest conditions were included to mitigate the low power inherent to several between-groups contrasts (i.e., Addiction vs. Healthy Controls). We chose to limit our literature review to experiments that only used the n-back paradigm to hold the task and cognitive process of interest (e.g., working memory) constant while assessing neurobiological variability related to different psychopathologies.

Neuroimaging experiments were included only if brain scans were acquired using whole-brain functional magnetic resonance imaging (fMRI) or positron emission tomography (PET). Only studies that reported whole-brain analyses, as opposed to region of interest (ROI) analyses, with coordinates listed in standard stereotactic space (MNI or Talairach/Tournoux), were included in our subsequent ALE analyses. All MNI coordinates were converted to Talairach coordinates (19) using a transformation created by Lacadie et al. (20).

Our minimum statistical criteria for inclusion consisted of studies with a significance threshold of $p < 0.001$ uncorrected in at least 8 individuals (Eickhoff, personal communication, 2016). In total, we identified 160 experiments that matched our criteria, comprised of 54 control, 20 Addiction, 17 ADHD, 25 Bipolar, 15 MDD, and 29 schizophrenia experiments. These

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157 experiments reported 1,603 brain activation foci obtained from a total of 4,509 participants. Our
158 search procedure was concluded in October of 2019.

159 **Activation Likelihood Estimation Algorithm**. To examine the brain regions activated
160 during the n-back task across addiction, ADHD, bipolar disorder, MDD, and schizophrenia
161 psychopathologies, we performed a coordinate-based meta-analysis using GingerALE v3.0.2
162 (17). GingerALE's revised ALE algorithm creates a statistical map using the supplied peak
163 coordinates to estimate the likelihood of activation of each voxel in the brain. Activation foci are
164 viewed as centers of 3-D Gaussian probability distribution functions, which are used to estimate
165 the probability that at least one of the activation foci in the dataset actually lies within a given
166 voxel (12) – these probabilities are known as Activation Likelihood Estimate (ALE) values.
167 Importantly, the ALE algorithm weighs the between-subject variance by the number of subjects
168 in each study, such that larger studies are associated with narrower Gaussian distributions than
169 smaller studies. Maps were then created using the voxel-wise ALE values for each contrast. The
170 resulting ALE maps were thresholded at $p < 0.01$ uncorrected and then subjected to a
171 permutation test (1000 replications) with a cluster threshold value $p < 0.01$ FWE (family-wise
172 error).

173 **Contrasts**. We conducted multiple ALE meta-analyses, both within and between-groups.
174 Initially, we characterized the n-back working memory network separately for healthy controls,
175 all psychopathologies collapsed, and for each individual psychopathology (i.e. within-group
176 contrasts). In the healthy controls contrast, we examined coordinates from 54 experiments,
177 comprising a total of 1,040 healthy control participants and 561 foci. We only included
178 publications that obtained data from healthy participants and were additionally used in the
179 within-group 'psychopathologies' contrasts. In the psychopathologies contrasts, we included data

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from a total of 106 experiments: 20 Addiction, 17 ADHD, 25 Bipolar, 15 MDD, and 29 schizophrenia. These experiments included a total of 1,042 foci and 3,469 participants. Next, we evaluated brain networks that were hyperactive in controls compared to all combined psychopathologies during the n-back task (i.e. between-group contrasts) and also compared individually as follow-up. A total of 73 experiments fit eligibility criteria for this analysis: 8 Controls > Addiction, 12 Controls > ADHD, 15 Controls > Bipolar, 11 Controls > MDD experiments, and 27 Controls > Schizophrenia; resulting in 336 foci from 2,788 participants. Lastly, we examined the brain networks that were hyperactive during the n-back task across all psychopathologies combined and individually, in comparison to healthy controls. For this analysis, we isolated 81 experiments that matched our criteria: 32 schizophrenia > controls, 18 bipolar > controls, 11 MDD > controls, 11 addiction > controls, and 9 ADHD > controls; consisting of 281 foci obtained from 2,629 participants. A full list of studies included in our within- and between-groups contrasts are available in Tables 1 and 2, respectively. For all analyses and contrasts, we report anatomical labels (Talairach Nearest Grey Matter) of the weighted center (x,y,z) of each obtained cluster. Clusters were overlaid onto the standard "Colin" brain in Talairach space (21) using Mango v. 4.1 software (http://ric.uthscsa.edu/mango/).

RESULTS

N-back working memory network within each group

To identify brain regions in healthy individuals and in those with psychopathology that increase in activation with increasing working memory load during the n-back, we conducted separate within-group meta-analyses. We first collapsed data across all healthy participants that were included in any of the undermentioned contrasts. Healthy participants activated an array of

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regions typically associated with prior examinations of working memory during the n-back paradigm (22,23). These regions included bilateral inferior parietal lobule (IPL) extending to precuneus, bilateral insula, bilateral declive of the cerebellum, bilateral mid frontal gyrus (MFG), left precentral gyrus extending into the anterior cingulate, right superior frontal gyrus (SFG), left ventral anterior nucleus of the thalamus extending to the mediodorsal nucleus, and bilateral tuber of the cerebellum (Figure 1, first row; Table 3).

We furthermore collapsed data across all within-group psychopathologies contrasts. We found convergence of activation in a breadth of brain regions, including bilateral SFG, bilateral MFG, bilateral IPL, right IFG, bilateral cerebellar declive, left precentral gyrus, left claustrum, left cingulate gyrus, right insula, left caudate, and left putamen (Figure 1, second row; Table 3).

Across many of the psychopathologies the topology of the ALE maps related to an increase in activation with increasing working memory load was consistent with that observed in the healthy participants and each other. For example, when considering individuals with addiction, increased working memory load was associated with increased activation in left cingulate gyrus, left sub-gyral (Brodmann area [BA] 6), bilateral superior parietal lobule (SPL), bilateral IPL, bilateral MFG, and bilateral precentral gyrus (Figure 1, third row; Table 3).

In the ADHD group, the n-back working memory network was characterized by activation in left SFG, left cingulate gyrus, right medial frontal gyrus (MeFG), left precentral gyrus, bilateral MFG, right IPL, right sub-gyral (BA 40), and left cerebellar declive (Figure 1, fourth row; Table 3).

In individuals with Bipolar Disorder, increased working memory load resulted in increased activation in bilateral IPL, left angular gyrus, bilateral MFG, left MeFG, left SFG, left

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cingulate gyrus, bilateral precentral gyrus, right claustrum, and right inferior frontal gyrus (IFG) (Figure 1, fifth row; Table 3).

In MDD, increased working memory load was associated with increased activation in bilateral IPL, right superior temporal gyrus (STG), bilateral precuneus, left angular gyrus, and left MFG (Figure 1, sixth row; Table 3).

In the schizophrenia group, increased working memory load during the n-back task was associated with activation in bilateral IPL, right angular gyrus, bilateral SPL, bilateral MFG, bilateral IFG, bilateral precentral gyrus, right cingulate gyrus, left MeFG, right anterior cingulate, right SFG, right insula, left inferior temporal gyrus (ITG), left fusiform gyrus, bilateral cerebellar declive, and left cerebellar culmen. (Figure 1, sixth row; Table 3).

Greater working memory-related activations in healthy individuals

To evaluate what brain regions showed greater working memory-related activations in healthy individuals compared to psychopathology more generally and maximize our power to detect an effect, we collapsed data across all between-group contrasts (Healthy Controls > Psychopathology) for the subsequent meta-analysis. Healthy individuals demonstrated greater activation in bilateral precuneus and right IFG (triangularis/opercularis) extending into insula (Figure 2, Table 3). Healthy participants from all studies contributed to the formation of the bilateral precuneus cluster, while subjects from MDD and schizophrenia studies contributed to the formation of the right IFG cluster.

Follow-up analyses examined the same comparisons – brain regions that exhibit greater n-back working memory-related activation in healthy subjects compared to those with a psychiatric diagnosis – but for each psychopathology separately. Across addiction studies, healthy subjects exhibited greater working memory-related activation than patients in left

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precuneus. Compared to individuals with ADHD, healthy controls exhibited greater activation in right MFG. Relative to those with bipolar disorder, healthy controls exhibited greater activation in left MFG. No brain regions exhibited significantly greater activation in healthy controls compared to individuals with MDD. Right IFG, insula, cerebellar culmen, nodule, and declive all exhibited greater activation in healthy controls compared to individuals with schizophrenia on the n-back task (Figure 3, Table 3).

Greater working memory related activations in individuals with psychopathology

We conducted an additional meta-analysis to examine effects in which patients across psychopathologies exhibited greater activations relative to controls during the n-back task (i.e. Psychopathology > Healthy Controls). We observed a significant convergence of hyperactivation across all psychopathologies compared to controls in the left anterior cingulate cortex/medial prefrontal cortex (lACC/mPFC) (Figure 2, Table 3). This cluster (-4, 36, -2) was centered in a central or hub region of the default mode network (DMN), a group of brain regions that are more active during rest than during task performance (24,25). Experiments from the addiction, ADHD, bipolar disorder, MDD, and schizophrenia greater than controls contrasts contributed to the formation of this cluster.

We next conducted a follow-up meta-analysis to examine effects in which patients across individual psychopathologies exhibited greater activations relative to controls during the n-back task. The ALE algorithm yielded no significant regions of convergence where participants diagnosed with addiction, ADHD, or MDD exhibited greater activation during the n-back working memory task compared to controls. In contrast, patients diagnosed with bipolar disorder

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and schizophrenia exhibited greater activation in the lACC extending into the mPFC during the n-back task compared to healthy controls (Figure 4, Table 3).

DISCUSSION

Deficits in working memory are commonly reported in individuals with a variety of psychopathologies. We examined neuroimaging data across ADHD, addiction, bipolar disorder, MDD, and schizophrenia to identify similarities and differences in human brain activation during the same working memory paradigm (n-back task). Elucidating convergent and/or divergent neurobiological correlates may shed light on their underlying pathophysiology (1–6). With increasing working memory load participants with psychiatric disorders when compared to controls exhibited hyperactivity in the mPFC, a hub of the DMN, while controls showed greater activation in the right IFG and bilateral precuneus. These results provide novel and compelling evidence that in addition to frontal and parietal dysfunction, DMN intrusion may constitute a conserved mechanism of dysregulation across psychopathologies resulting in poorer working memory performance.

Patterns of activation with increasing working memory load in each group were remarkably consistent following our within-group meta-analyses. Prototypical regions – including the bilateral IPL, bilateral MFG, bilateral anterior insula, and SFG – extending ventrally into the anterior cingulate cortex – were seen within each group and are consistent with prior meta-analytic studies examining working memory load in non-patient populations (22,23). The lack of grossly discernable differences is not entirely unexpected given that impairments in behavior often result in subtle, rather than large scale, changes in functional activity.

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While some qualitative differences in the topology of ALE activations were evident across groups, we believe these dissimilarities arise from differences in power across contrasts. For example, the within-group psychopathologies contrast had the most statistical power (106 experiments, 1042 foci); thus, it follows that the working memory network for this contrast should be more robust than in the MDD contrast, which had the least power (15 experiments, 142 foci). Finally, we note that while there are observable differences in the within-group, collapsed controls contrast versus psychopathologies contrast (for example, in bilateral MFG), regions of spatial convergence or divergence do not represent direct statistical comparisons. To accomplish this, meta-analyses should be conducted on publications with between-group statistical comparisons that include both patient and healthy control samples. Accordingly, meta-analyses comparing between-group differences are essential for identifying convergence and divergence of activations related to working memory impairments in psychiatric disorders.

To directly examine functional differences between healthy controls and subjects with psychopathology as working memory load increases, we performed meta-analyses of between-groups data. These analyses detailed regions in healthy subjects that exhibited greater working memory load-related activation relative to those with psychopathology, and vice versa. Considerable heterogeneity in activations were evident across groups which likely reflects differences in power across the different psychopathologies (as noted above). However, it is possible that the observed differences may highlight unique functional impairments for each psychopathology when compared to healthy individuals. We focus our discussion, rather, on the undermentioned collapsed data, which sheds insight into common pathophysiology across all disease states and is bolstered by greater statistical power.

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To examine common neurobiological correlates, we first collapsed across all contrasts to examine brain regions in which healthy subjects exhibited greater working memory load-related activation than individuals with any given psychopathology. With this analysis, we were able to examine brain regions that exhibited hyperactivity in healthy controls relative to individuals with mental illness, who are typically impaired on the n-back task. We found convergence of activation in bilateral precuneus and right IFG extending into insula. The precuneus has long been implicated in successful episodic memory retrieval (26,27), and is associated with better performance on spatial working memory tasks (28,29). Further, it has been shown to activate during the n-back in healthy subjects regardless of memory load, object, age, or gender (23). Differential recruitment of bilateral precuneus in this instance requires further investigation, though we posit that its greater recruitment is coincident with normal cognitive processing during this task. The IFG/insula region is a component of the salience network, a group of brain regions responsible for orienting toward behaviorally salient external events (30,31). While insula is implicated in disparate cognitive responses such as emotional and interoceptive processing, in this instance it is likely responsible for orienting toward salient stimuli and switching between networks (DMN and central executive) to permit access to attention and working memory stores (32,33). We thus assert that, in healthy participants, greater insula recruitment likely reflects an "open door policy" for working memory that is 'shut' in those with psychopathology.

While working memory impairments may arise from aberrant salience detection, behavioral performance may also suffer due to spurious activations of regions unrelated to the task at hand. Supporting this possibility, individuals with psychopathology compared to healthy controls during the n-back task exhibited greater activation with increasing working memory

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load in the mPFC. When data from all psychopathologies was collapsed, the cluster was comprised of approximately 14.8% MDD studies, 37.0% Bipolar studies, 33.3% schizophrenia studies, 11.11% addiction studies, and 3.7% ADHD studies. When examining each psychopathology separately subjects with schizophrenia and bipolar disorder both exhibited a similar cluster that survived corrections for multiple comparisons, while data from ADHD, addiction, and MDD groups did not survive statistical thresholding. Thus, pooling across psychopathologies helped identify the ADHD, addiction, and MDD groups as contributors to the mPFC cluster, while on their own not significant.

The mPFC is critical for a diverse array of functions in the brain. Lesions in this region are associated with drastic impairments in personality, affect, emotion, decision-making, and general cognition (34). Literature linking aberrant mPFC function to psychiatric disorders is replete. For example, structural analyses suggest that mPFC-amygdala white matter connectivity predicts anxiety and depressive symptoms in childhood (35), and functional connectivity between these regions is negatively correlated with PTSD symptoms (36). Smaller mPFC volume in adolescents predicts ADHD symptoms after 5 years, while mPFC activity in individuals with schizophrenia and comorbid nicotine addiction (relative to healthy controls) is enhanced following exposure to cigarette cues (37). Finally, a recent meta-analysis supports the assertion that distinct subregions of the mPFC are associated with psychopathologies such as PTSD, addiction, depression, social anxiety, and schizophrenia (38). Of note, the mPFC plays an integral role in memory; indeed, those with mPFC lesions are prone to memory confabulations, poor schematic memory, and impaired environmental context effects on memory formation (34). mPFC-hippocampal interactions have been shown to mediate memory-based decision-making (39,40) as well. Further, psychophysiological analyses during a working memory task support

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the role of mPFC as an "emotional gating" mechanism in instances of high cognitive load (41). Indeed, this supports the earlier thesis that mPFC connectivity facilitates emotion-cognition interactions, or simply, the interplay between affect and reason (42).

In addition to being a key region responsible for the integration of cognitive and emotional stimuli, the mPFC is also a known hub of the DMN – an organized network of brain regions that are more active during rest than during cognitive tasks (24,43). Intrusion of the DMN during cognitive tasks may reflect insufficient top-down attentional control, leading to performance decrements (44). This "default mode interference hypothesis" suggests that spontaneous low frequency activity in regions of the DMN, such as the mPFC, can emerge during the performance of a task and occupy neural resources necessary for performing that task, ultimately resulting in behavioral impairments (45). Strikingly, Whitfield-Gabrieli et al. (46) examined patients with schizophrenia and first-degree relatives of those with schizophrenia, and found that those particular individuals exhibited reduced task-related suppression of a similar, though more anterior, region in mPFC during an n-back working memory paradigm. Whitfield-Gabrieli et al. (46) was not incorporated in our analyses as the data did not conform to our inclusion criteria. Our result provides further replication for the role of dysregulated mPFC activity as a direct contributor to poor working memory performance in schizophrenia and bipolar disorder, and suggests that it may have a role to play in ADHD, addiction, and MDD as well.

Conclusion

We have found evidence for greater recruitment of regions within the salience network (i.e. IFG and insula) in healthy individuals along with DMN (i.e. mPFC) intrusion in psychiatric patients during performance of the n-back working memory paradigm. Not only do these results

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provide evidence for the default mode interference hypothesis, they also speak more generally in support of the triple network model of Menon (47) which posits that aberrant function within three neurocognitive networks constitute a common feature among multiple psychopathologies. These three networks, the frontoparietal central executive network (CEN), salience network (SN), and default mode network (DMN) have been shown to be dysregulated in schizophrenia, depression, dementia, autism, and anxiety (47). We extend these findings to suggest that disruption in a combination of at least two of these networks, the DMN and SN, play a role in affecting working memory performance of individuals with schizophrenia and bipolar disorder, and that such a role may exist in ADHD, addiction, and MDD as well.

Limitations and Future Directions

In meta-analyses the recommended number of experiments per contrast is 20 (Eickhoff, personal communications). Here, we took great efforts to meet this recommendation, while at the same time stringently applying our inclusion/exclusion criteria to obtain the most accurate and interpretable results. On average, we had 30.21 experiments per contrast including pooled contrasts such as 'All Psychopathologies' 'Controls', and 'Psych > Con'. With pooled contrasts excluded, there were 17.33 experiments per contrast. With this in mind, however, the minimum number of experiments included was 8 in the Con > Addiction contrast. Caution should be taken in over-interpreting the related results. In fact, between-group contrasts of each psychopathology separately, which are the most informative to pathologically related differences in brain activation, had the fewest number of experiments on average (mean = 15.4). This notable limitation speaks to the need for replication studies and large sample sizes to facilitate the examination of between group differences. However, our approach to collapsing across psychopathologies was sufficiently powered and provided mechanistic insight to working

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406 memory impairments. As this meta-analysis captures cross-sectional data, further studies are
407 necessary to determine whether the observed differences in brain activity are a cause or
408 consequence of subjects' respective diagnoses. Finally, recent research has used the mPFC as a
409 target for fMRI-based neurofeedback (48). Future studies should determine whether this
410 approach is capable of mitigating working memory deficits in individuals with psychopathology.
411 (WORD COUNT: 4077)
412

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ACKNOWLEDGEMENTS

We would like to thank Drs. Simon Eickhoff and Mick Fox for their help in implementing the ALE algorithm, as well as Dr. Michael Cody Riedel for help with visualization. We would finally like to thank Candelaria Albarracin for help with data collection. This work was supported by startup funds provided by the Florida International University to A.T.M and by NIH R01-DA041353 (A.R.L.).

AUTHOR CONTRIBUTIONS

Conceptualization, A.T.M. and M.C.F.; Investigation, M.C.F.; Formal Analysis, M.C.F.; Writing – Original Draft Preparation, M.C.F.; Writing – Review and Editing, M.C.F., A.R.L., and A.T.M.; Supervision, A.T.M.; Funding Acquisition, A.T.M and A.R.L.

COMPETING INTERESTS

The authors declare no competing interests.

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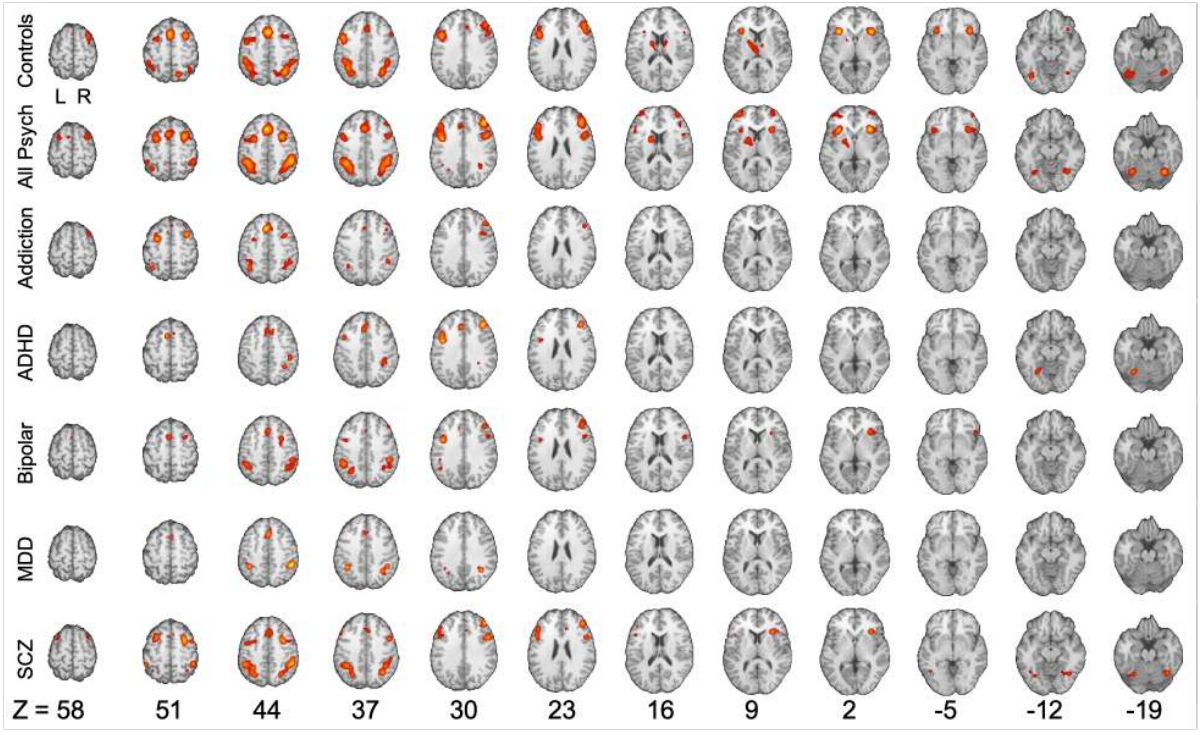

Figure 1. Within-group contrasts. From top to bottom are n-back working memory-related activations in healthy controls, participants with addiction, ADHD, bipolar disorder, major depressive disorder (MDD), and schizophrenia (SCZ). These analyses include data from a total of 160 experiments and 4509 subjects, from which 1603 foci were obtained.

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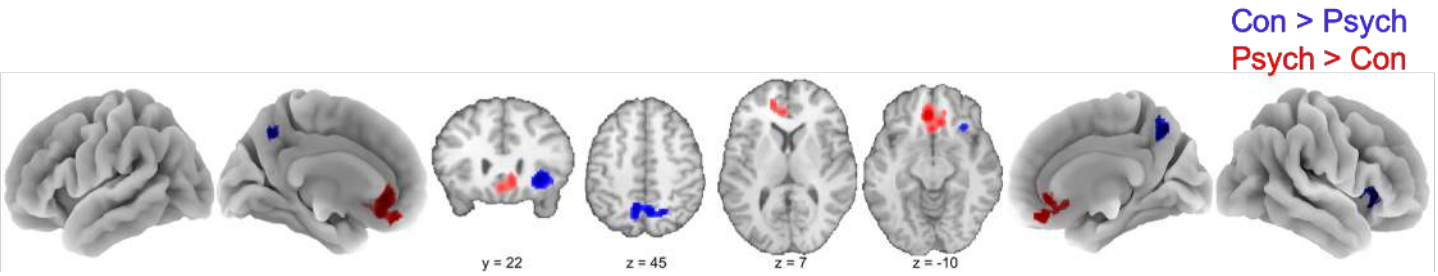

Figure 2. Between-group contrasts. Clusters show regions in which healthy controls exhibit greater activation than participants with psychopathologies (blue) or regions in which participants with psychopathologies demonstrate greater activation that healthy controls (red). The latter contrast converges in lACC/mPFC extending into OFC, while the prior contrast exhibits two clusters of convergence in precuneus and rIFG extending into insula. Darker colors indicate higher ALE values (and thus lower *p*-values). Con = Controls. Psych = All psychopathologies.

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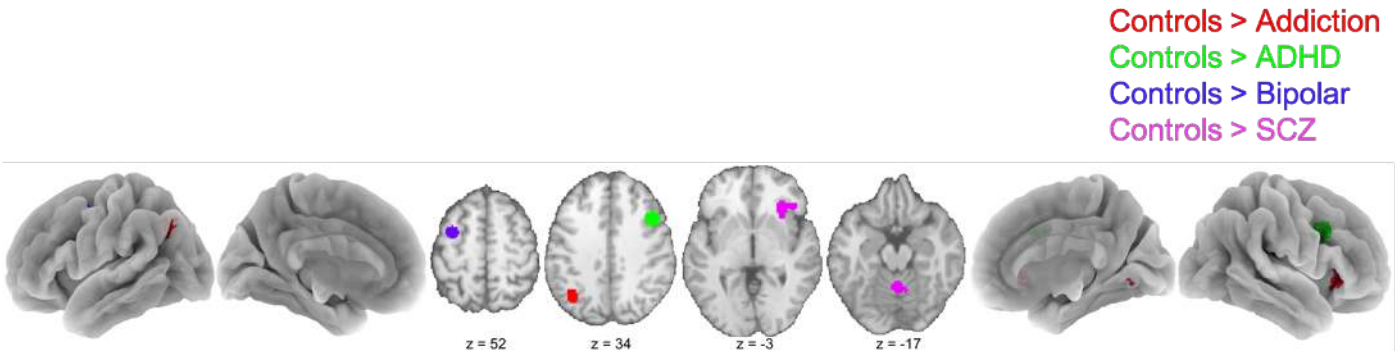

Figure 3. Between-group contrasts. Each contrast represents regions of n-back-related hyperactivation in healthy controls relative to participants with addiction (red), ADHD (green), bipolar disorder (blue), or schizophrenia (SCZ; pink). These regions included left precuneus, right MFG, left MFG, as well as right IFG (extending into insula) and cerebellum, respectively. No significant clusters were obtained for participants with major depressive disorder.

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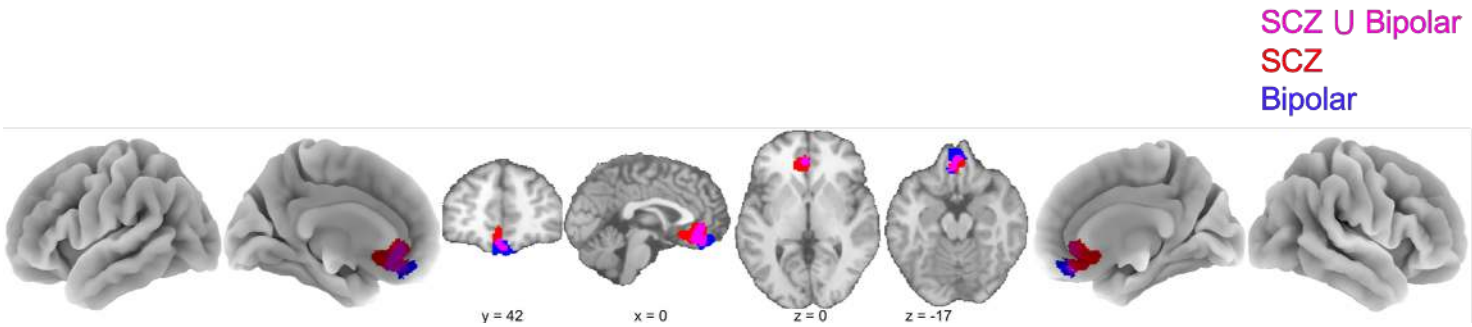

Figure 4. Between-group contrasts. Contrasts represent a region in the brain in which hyperactivity was observed in participants with schizophrenia (SCZ; red) or bipolar disorder (blue). These regions converge (pink) in lACC/mPFC, with a slight extension into orbitofrontal cortex.

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TABLE 1. WITHIN-GROUPS CONTRASTS

Publication	Contrast	Foci	N-back	Stimulus
Addiction				
Bustamante, 2011	Main activation 2-back>0-back, Cocaine	8	0,2	Letters (Auditory)
Campanella, 2013	2-back>0-back, Binge Drinkers	36	0,2	Numbers
Charlet, 2013	Functional activation 2-back>0-back, ADP	4	0,2	Numbers
Cousijn, 2013	2-back>0-back, Cannabis	3	0,2	Letters
Cousijn, 2013	2-back>1-back, Cannabis	4	1,2	Letters
Loughead, 2015	Parametric 3>2>1>0-back, Abstinent Smokers	9	0,1,2,3?	Fractals
McClernon, 2015	2-back>0-back, Placebo + Abstinent Smokers	8	0,2	Letters
Nichols, 2013	3-back>0-back, Abstinent Smokers	7	0,3	Letters
Owens, 2018	2-back>0-back, THC positive	19	0,2	Objects
Pfefferbaum, 2001	Areas of activation 2-back>rest, Alcoholics	19	rest,2	Dots
Schweinsburg, 2010	SWM 2-back>0-back, Marijuana Adolescents	14	0,2	Abstract Drawings
Sirnes, 2018	Word 2-back>1-back, Opioid-exposed children	1	1,2	Words of Stroop
Sirnes, 2018	Color 2-back>1-back, Opioid-exposed children	1	1,2	Colors of Stroop
Smith, 2010	Visuospatial 2-back>0-back, Marijuana	14	0,2	Dots
Sweet, 2010	2-back>0-back, Placebo + Abstinent Smokers	14	0,2	Letters
Tomasi, 2007	2-back>0-back, Abstinent cocaine abusers	21	0,2	Letters
Tomasi, 2007	0<1<2-back load, Abstinent cocaine abusers	7	0,1,2	Letters
Wesley, 2017	2-back>1-back, Non-dependent heavy drinkers	10	1,2	Letters
Wesley, 2017	2-back>1-back, Dependent heavy drinkers	5	1,2	Letters
Xu, 2005	0<1<2<3-back parametric, abstinent smokers	5	0,1,2,3	Letters
ADHD				
Bedard, 2014	Parametric load 0<1<2-back, ADHD children	11	0,1,2	Dots
Bedard, 2014	2-back>0-back, ADHD children	7	0,2	Dots
Chantiluke, 2015	2-back>0-back, ADHD boys + placebo	8	0,2	Letters
Chantiluke, 2015	3-back>0-back, ADHD boys + placebo	7	0,3	Letters
Cubillo, 2013	2-back>0-back, ADHD boys + Placebo	8	0,2	Letters
Cubillo, 2013	3-back>0-back, ADHD boys + placebo	6	0,3	Letters
*Ko, 2015	2-back>0-back, ADHD adults	10	0,2	Numbers
Ko, 2018	2-back>0-back, ADHD adults	12	0,2	Numbers
Li, 2014	Task-positive activation 2-back>fix, male ADHD	6	fixation,2	Images (Categorical)
Massat, 2012	2-back>0-back, ADHD children	16	0,2	Numbers
Mattfeld, 2016	2-back>0-back, persisted ADHD adults	4	0,2	Letters
Mattfeld, 2016	2-back>1-back, persisted ADHD adults	3	1,2	Letters
Mattfeld, 2016	3-back>0-back, persisted ADHD adults	5	0,3	Letters
Mattfeld, 2016	3-back>1-back, persisted ADHD adults	7	1,3	Letters
Mattfeld, 2016	3>2>1>0-back, persisted ADHD adults	5	0,1,2,3	Letters
Salavert, 2015	2-back>1-back, ADHD adults	1	1,2	Letters
Valera, 2005	2-back>0-back, unmedicated ADHD adults	9	0,2	Letters
Bipolar				
Brooks, 2015	0<1<2-back, depressed Bipolar II	19	0,1,2	Letters
Deckersbach, 2008	2-back>fixation, depressed Bipolar I	20	fixation,2	Letters
Drapier, 2008	2-back>0-back, Bipolar I patients	6	0,2	Letters
Drapier, 2008	3-back>0-back, Bipolar I patients	4	0,3	Letters
Fernandez-Corcuera, 2013	2-back>asterisk baseline, bipolar depressed	5	asterisk,2	Letters
Frangou, 2008	0<1<2<3-back, Bipolar I patients	15	0,1,2,3	Letters
Frangou, 2008	Effect of load 0<1<2<3-back, Bipolar I patients	1	load, 0,1,2,3	Letters
Haldane, 2008	0<1<2<3-back, Bipolar I + Lamotrigine	7	parametric, 0,1,2,3	Letters
Jogia, 2012	3-back>0-back, Euthymic Bipolar I patients	5	0,3	Letters
Macoveanu, 2018	2-back>0-back, Bipolar patients	14	0,2	Dots

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Macoveanu, 2018	2-back>0-back, Bipolar patients	23	1,2	Dots
Miskowiak, 2017	2-back>1-back, adult Bipolar I outpatients	13	1,2	Shapes
Monks, 2004	2-back>0-back, male Bipolar Disorder I	16	0,2	Letters
Pomarol-Clotet, 2012	2-back> asterisk baseline, Manic bipolar patients	11	asterisk,2	Letters
Pomarol-Clotet, 2015	2-back>1-back, Bipolar I and II - depressed	11	1,2	Letters
Pomarol-Clotet, 2015	2-back>1-back, Bipolar I - manic	8	1,2	Letters
Pomarol-Clotet, 2015	2-back>baseline, Bipolar I and II - depressed	7	asterisk,2	Letters
Pomarol-Clotet, 2015	2-back> baseline, Bipolar I - manic	11	asterisk,2	Letters
Pomarol-Clotet, 2015	2-back>1-back, Bipolar I - euthymic	5	1,2	Letters
Pomarol-Clotet, 2015	2-back>baseline, Bipolar I – euthymic	2	asterisk,2	Letters
Rodriguez-Cano, 2017	2-back> flashing asterisk, Bipolar patients	2	asterisk,2	Letters
Thermenos, 2009	2-back>0-back, Bipolar outpatients	5	0,2	Letters
Townsend, 2010	2-back>0-back, Bipolar I - depressed	20	0,2	Letters
Townsend, 2010	2-back>0-back, Bipolar I - manic	15	0,2	Letters
Townsend, 2010	2-back>0-back, Bipolar I – euthymic	4	0,2	Letters
MDD				
Bartova, 2015	Main effect of activation 2-back>0-back, rMDD	9	0,2	Numbers
Garrett, 2011	2-back>0-back, psychotic Major Depression	15	0,2	Letters
Garrett, 2011	2-back>0-back, nonpsychotic Major Depression	5	0,2	Letters
*Harvey, 2005	1,2,3-back>0-back, unipolar depressive disorder	8	0,2	Letters
Marquand, 2008	Regions contributing to depression during 2-back	18	0,2	Letters
Matsuo, 2007	2-back>1-back, Major Depressive Disorder	7	1,2	Numbers
Matsuo, 2007	2-back>0-back, Major Depressive Disorder	3	0,2	Numbers
Miskowiak, 2016	2-back>0-back, MDD patients	6	0,2	Dots
Miskowiak, 2016	2-back>1-back, MDD patients	4	1,2	Dots
Norbury, 2013	1,2,3-back>0-back, unmedicated rMDD	5	0,1,2,3	Letters
Rodriguez-Cano, 2014	2-back>flashing asterisk, MDD patients	9	asterisk,2	Letters
Rodriguez-Cano, 2017	2-back> flashing asterisk, MDD patients	3	asterisk,2	Letters
Rose, 2006	Linear increase over 0,1,2,3-back, MDD patients	9	0,1,2,3	Dots
Schoning, 2009	2-back>1-back, MDD inpatients	28	1,2	Letters
Schoning, 2009	2-back>0-back, MDD inpatients	13	0,2	Letters
Schizophrenia				
Guerrero-Pedraza, 2012	2-back>1-back, Non-affective psychosis	7	1,2	Letters
Guerrero-Pedraza, 2012	2-back>asterisk, Non-affective psychosis	6	asterisk,2	Letters
Guimond, 2018	2-back>0-back, schizophrenic patients	7	0,2	Letters and Faces
Honey, 1999	2-back>0-back, chronic male schizophrenics	11	0,2	Letters
Honey, 2002	2-back>0-back, chronic male schizophrenics	7	0,2	Letters
Honey, 2003	2-back>0-back, schizophrenic patients	13	0,2	Letters
Kim, 2003	2-back>0-back, schizophrenic patients	7	0,2	Shapes
Kumari, 2006	2-back>0-back, non-violent schizophrenic males	18	0,2	Dots
Kumari, 2006	2-back>0-back, violent schizophrenic males	10	0,2	Dots
Kumari, 2009	2-back>rest, schizophrenics (CBT+ TAU)	16	rest,2	Dots
Kumari, 2009	2-back>0-back, schizophrenics (CBT + TAU)	12	0,2	Dots
Li, 2019	2-back>0-back, schizophrenic patients	19	0,2	Shapes and Auditory
Madre, 2013	2-back>asterisk, schizo-affective patients	8	asterisk,2	Letters
Mendrek, 2004	2-back>0-back, stable schizophrenic outpatients	13	0,2	Letters
Nejad, 2011	2-back>1-back, schizophrenic patients	24	1,2	Letters
Nejad, 2011	2-back>0-back, schizophrenic patients	23	0,2	Letters
Perlstein, 2001	load main effect 0,1,2-back, schizophrenics	10	0,1,2	Letters
Royer, 2009	2-back>0-back, schizophrenic patients	21	0,2	Letters
Sapara, 2013	2-back>rest, preserved insight schizophrenics	13	rest,2	Dots
Sapara, 2013	2-back>rest, poor insight schizophrenics	10	rest,2	Dots
Sapara, 2013	2-back>0-back, preserved insight schizophrenics	9	0,2	Dots
Scheuerecker, 2008	2-back(d)>0-back(d), untreated schizophrenics	11	0,2 degraded	Letters
Scheuerecker, 2008	2-back>0-back, untreated schizophrenics	7	0,2	Letters
Surguladze, 2007	3-back>0-back, schizophrenia + RLAI	5	0,3	Letters

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Surguladze, 2007	2-back>0-back, schizophrenia + RLAI	4	0,2	Letters
Surguladze, 2007	3-back>0-back, schizophrenia + CONV	2	0,3	Letters
Surguladze, 2007	2-back>0-back, schizophrenia + CONV	2	0,2	Letters
Tan, 2006	2-back>1-back, schizophrenic patients	9	1,2	Numbers
Yoo, 2005	2-back>0-back, schizophrenic patients	17	0,2*	Faces
Controls				
Bedard, 2014	linear trend across 0,1,2-back, healthy children	7	0,1,2	Dots
Bedard, 2014	2-back>0-back, healthy children	7	0,2	Dots
Bustamante, 2011	2-back>0-back, male matched controls	12	0,2	Letters (Auditory)
Campanella, 2013	2-back>0-back, undergraduate student controls	19	0,2	Numbers
Chantiluke, 2015	3-back>0-back, healthy matched boys	7	0,3*	Letters
Cubillo, 2013	3-back>0-back, healthy control boys	8	0,3	Letters
Cubillo, 2013	2-back>0-back, healthy control boys	7	0,2	Letters
Deckersbach, 2008	2-back>fixation, healthy control females	12	fixation,2	Letters
Drapier, 2008	3-back>0-back, matched controls	7	0,3	Letters
Drapier, 2008	2-back>0-back, matched controls	6	0,2	Letters
Fernandez-Corcuera, 2013	2-back>flashing asterisk, matched controls	2	asterisk,2	Letters
Frangou, 2008	3>2>1>0-back, matched controls	11	0,1,2,3	Letters
Garrett, 2011	2-back>0-back, healthy comparison subjects	11	0,2	Letters
Guimond, 2018	2-back>0-back, healthy controls	8	0,2	Letters and Faces
Harvey, 2005	1,2,3-back>0-back, right-handed control subjects	10	0,2	Letters
Honey, 1999	2-back>0-back, right-handed male controls	12	0,2	Letters
Honey, 2002	2-back>0-back, right-handed matched controls	10	0,2	Letters
Honey, 2003	2-back>0-back, healthy volunteers	11	0,2	Letters
Jogia, 2012	3-back>0-back, healthy controls	5	0,3	Letters
Kim, 2003	2-back>0-back age and sex matched volunteers	8	0,2	Shapes
Kumari, 2006	2-back>0-back, healthy nonviolent men	18	0,2	Dots
Kumari, 2009	2-back>rest, healthy participants	12	rest,2	Dots
Kumari, 2009	2-back>0-back, healthy participants	12	0,2	Dots
Li, 2014	2-back>fixation, right-handed healthy males	3	fixation,2	Images (Categorical)
Li, 2019	2-back>0-back, healthy controls	9	0,2	Shapes and Auditory
Marquand, 2008	2-back>0-back, right-handed controls	19	0,2	Letters
Massat, 2012	2-back>0-back, healthy volunteers	17	0,2	Numbers
Matsuo, 2007	2-back>0-back, healthy controls	2	0,2	Numbers
Mendrek, 2004	2-back>0-back, healthy controls	12	0,2	Letters
Monks, 2004	2-back>0-back, healthy male volunteers	17	0,2	Letters
Norbury, 2013	3>2>1>0-back, healthy controls	6	0,1,2,3	Letters
Pfefferbaum, 2001	2-back>match-to-center, control men	30(28?)	center,2	Dots
Pfefferbaum, 2001	2-back>rest, control men	14	rest,2	Dots
Pomarol-Clotet, 2012	2-back>flashing asterisk, matched controls	2	asterisk,2	Letters
Rodriguez-Cano, 2014	2-back>flashing asterisk, healthy controls	8	asterisk,2	Letters
Rodriguez-Cano, 2017	2-back>flashing asterisk, healthy controls	1	asterisk,2	Letters
Royer, 2009	2-back>0-back, matched adults	18	0,2	Letters
Sapara, 2013	2-back>rest, matched healthy participants	16	rest,2	Dots
Sapara, 2013	2-back>0-back, matched healthy participants	6	0,2	Dots
Scheuerecker, 2008	2-back>0-back, healthy controls	15	0,2	Letters
Scheuerecker, 2008	2-back degraded>0-back degraded, controls	8	0,2-degraded	Letters
Schoning, 2009	2-back>0-back, healthy control participants	20	0,2	Letters
Schoning, 2009	2-back>1-back, healthy control participants	7	1,2	Letters
Sirnes, 2018	Word 2-back>1-back, control participants	7	1,2	Words of Stroop
Sirnes, 2018	Color 2-back>1-back, control participants	8	1,2	Color of Stroop
Smith, 2010	2-back>0-back, non-using controls	14	0,2	Dots
Surguladze, 2007	3-back>0-back, healthy control volunteers	3	0,3	Letters
Surguladze, 2007	2-back>0-back, healthy control volunteers	3	0,2	Letters
Tan, 2006	2-back>1-back, healthy comparison subjects	7	1,2	Numbers
Tomasi, 2007	2-back>0-back, matched healthy controls	18	0,2	Tomasi

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Townsend, 2010	2-back>0-back, healthy control subjects	15	0,2	Letters
Valera, 2005	2-back>0-back, healthy control subjects	5	0,2	Letters
Wesley, 2017	2-back>1-back, control participants	7	1,2	Letters
Yoo, 2005	2-back>0-back, matched healthy volunteers	22	0,2*	Faces

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TABLE 2. BETWEEN-GROUPS CONTRASTS

Publication	Contrast	Foci	N-back	Stimulus
Addiction > Controls				
Campanella, 2013	2-back>0-back, binge drinkers>controls	2	0,2	Numbers
Charlet, 2013	2-back>0-back, detoxified ADP>controls	12	0,2	Numbers
Padula, 2007	2-back>0-back, abstinent MJ>controls	3	0,2	Abstract Shapes
Sirnes, 2018	2-back>1-back, opioid-exposed children	2	1,2	Colors
Sirnes, 2018	2-back>1-back, opioid-exposed children	1	1,2	Words
Smith, 2010	2-back>0-back, MJ>controls	3	0,2	Dots
Tomasi, 2007	2-back>0-back, Cocaine>controls	11	0,2	Letters
Tomasi, 2007	2>1>0-back, Cocaine>controls	1	0,1,2 load	Letters
Wesley, 2017	2-back>1-back, Alcohol-dependent>Controls	1	1,2	Letters
Addiction < Controls				
Bustamante, 2011	2-back>0-back, controls>cocaine-dependent	1	0,2	Letters (Auditory)
Daumann, 2003	2-back>rest, controls>heavy MDMA users	1	rest,2	Letters
Daumann(2), 2003	2-back>rest, controls> heavy MDMA users	1	rest,2	Letters
Livny, 2018	2-back>0-back, controls>synthetic cannabinoid	1	0,2	Letters
Livny, 2018	2-back>1-back, controls> synthetic cannabinoid	2	1,2	Letters
Pfefferbaum, 2001	2-back>rest, controls>chronic alcoholics	24	rest,2	Dots
Tomasi, 2007	2-back>0-back, controls>cocaine abusers	10	0,2	Letters
Tomasi, 2007	2>1>0-back, controls>cocaine abusers	2	0,1,2 load	Letters
ADHD > Controls				
Bedard, 2014	2-back>0-back, ADHD youth>controls	2	0,2	Dots
Cubillo, 2013	3>2>1>0-back, ADHD+MPH boys>controls	1	0,1,2,3 load	Letters
Ko, 2015	2-back>0-back, ADHD adults>controls	2	0,2	Numbers
Ko, 2018	2-back>0-back, ADHD adults>controls	3	0,2	Numbers
Li, 2014	2-back>fixation, ADHD males>controls	3	fixation,2	Images (Categorical)
Mattfeld, 2016	2-back>1-back, ADHD adults>controls	1	1,2	Letters
Mattfeld, 2016	3-back>1-back, ADHD adults>controls	1	1,3	Letters
Mattfeld, 2016	3-back>2-back, ADHD adults>controls	2	3,2	Letters
Salavert, 2015	2-back>asterisk, ADHD adult patients>controls	1	asterisk,2	Letters
ADHD < Controls				
Bayerl, 2010	2-back>0-back, controls>adult ADHD patients	1	0,2	Letters
Brown, 2012	2-back>0-back, controls>male ADHD+BPD	2	0,2	Letters
Cubillo, 2013	3>2>1>0-back, controls> ADHD+MPH boys	1	0,1,2,3 load	Letters
Cubillo, 2013	3>2>1>0-back, controls>ADHD+ATX boys	1	0,1,2,3 load	Letters
Kobel, 2009	3+2>0-back, controls>ADHD boys	5	2,3*	Numbers
Mattfeld, 2016	2-back>0-back, controls>ADHD adults	2	0,2	Letters
Mattfeld, 2016	3-back>0-back, controls>ADHD adults	1	0,3	Letters
Mattfeld, 2016	3>2>1>0-back, controls>ADHD adults	1	0,1,2,3	Letters
Mattfeld, 2016	3>2>1>0-back, controls>impaired ADHD adults	5	0,1,2,3	Letters
Valera, 2005	2-back>0-back, controls>ADHD adults	2	0,2	Letters
Valera, 2005	2-back>0-back, controls>ADHD-LD adults	1	0,2	Letters
Valera, 2010	2-back>0-back, controls> ADHD adults	2	0,2	Letters
Bipolar > Controls				
Adler, 2004	2-back>0-back, Bipolar patients>controls	8	0,2	Numbers
Alonso-Lana, 2016	2-back>asterisk, euthymic bipolar>controls	1	asterisk,2	Letters
Alonso-Lana, 2019	2-back>asterisk, manic bipolar>controls	1	asterisk,2	Letters
Alonso-Lana, 2019	2-back>asterisk, euthymic bipolar>controls	1	asterisk,2	Letters
Alonso-Lana, 2019	2-back>1-back, manic bipolar>controls	1	1,2	Letters
Deckersbach, 2008	2-back>fixation, Bipolar I disorder>control	4	fixation,2	Letters
Dima, 2016	3-back>0-back, Bipolar patients>control	3	0,3	Letters

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Drapier, 2008	2-back>0-back, Bipolar I patients>controls	2	0,2	Letters
Fernandez-Corcuera, 2013	2-back>asterisk, Bipolar depressed>controls	1	asterisk,2	Letters
Frangou, 2017	3-back>0-back, BD I patients>relatives+controls	1	0,3	Letters
Jogia, 2012	3-back>0-back, euthymic BD I>Controls	4	0,3	Letters
Monks, 2004	2-back>0-back, Bipolar disorder I>Controls	3	0,2	Letters
Pomarol-Clotet, 2012	2-back>asterisk, manic bipolar>controls	3	asterisk,2	Letters
Pomarol-Clotet, 2015	2-back>asterisk, Bipolar I manic>controls	1	asterisk,2	Letters
Pomarol-Clotet, 2015	2-back>asterisk, Bipolar I/II depressed>controls	1	asterisk,2	Letters
Pomarol-Clotet, 2015	2-back>asterisk, Bipolar I euthymic> controls	1	asterisk,2	Letters
Rodriguez-Cano, 2017	2-back>asterisk, Bipolar I patients>controls	1	asterisk,2	Letters
Thermenos, 2009	2-back>0-back, bipolar outpatients>controls	1	0,2	Letters
Bipolar < Controls				
Alonso-Lana, 2019	2-back>asterisk, controls> manic bipolar	2	asterisk,2	Letters
Alonso-Lana, 2019	2-back>1-back, controls>euthymic bipolar	1	1,2	Letters
Brooks, 2015	2>1>0-back(load), controls>Bipolar II depressed	8	0,1,2	Letters
Dima, 2016	3-back>0-back, controls>Bipolar patients	4	0,3	Letters
Fernandez-Corcuera, 2013	2-back>asterisk, controls>Bipolar depressed	3	asterisk,2	Letters
Frangou, 2017	3-back>0-back, relatives+controls> BD I patients	1	0,3	Letters
Jogia, 2012	3-back>0-back, controls>euthymic BD I	1	0,3	Letters
Monks, 2004	2-back>0-back, controls>bipolar disorder I	7	0,2	Letters
Moser, 2018	2-back>0-back, controls>bipolar disorder	3	0,2	Objects
Meusel, 2013	2-back>0-back, controls>MDD+BD	1	0,2	Abstract Objects
Pomarol-Clotet, 2012	2-back>asterisk, controls>manic bipolar	3	asterisk,2	Letters
Pomarol-Clotet, 2015	2-back>asterisk, controls> Bipolar I manic	6	asterisk,2	Letters
Pomarol-Clotet, 2015	2-back>asterisk, controls>Bipolar I/II depressed	3	asterisk,2	Letters
Rodriguez-Cano, 2017	2-back>asterisk, controls>Bipolar I patients	2	asterisk,2	Letters
Thermenos, 2009	2-back>0-back, controls> bipolar outpatients	1	0,2	Letters
MDD > Controls				
Bartova, 2015	2-back>0-back, remitted MDD patients>controls	4	0,2	Numbers
Fitzgerald, 2008	2-back>0-back, MDD>healthy controls	20	0,2	Letters
Harvey, 2005	2-back>0-back, nonpsychotic MDE>controls	3	0,2	Letters
Matsuo, 2007	2-back>1-back, recurrent MDD>healthy controls	2	1,2	Numbers
Nord, 2018	3-back>1-back, MDD patients>controls	1	1,3	Letters
Nord, 2018	3-back>1-back, MDD patients>relatives	12	1,3	Letters
Rodriguez-Cano, 2014	2-back>asterisk, MDD>controls	1	asterisk,2	Letters
Rodriguez-Cano, 2017	2-back>asterisk, MDD>controls	1	asterisk,2	Letters
Rose, 2006	3>2>1>0-back (linear increase), MDD>Controls	1	0,1,2,3	Dots
Schoning, 2009	2-back>0-back, euthymic MDD>Controls	8	0,2	Letters
Yüksel, 2018	3-back>2-back, MDD patients>Controls	1	2,3	Letters
MDD < Controls				
Barch, 2003	2-back>fixation, controls>unipolar MDD	4	fixation,2	Words and Faces
Dumas, 2014	2-back>0-back, controls>MDD old adults	3	0,2	Verbal
Frangou, 2017	3-back>0-back, controls>MDD	1	0,3	Letters
Ionescu, 2015	2-back>1-back, controls>treatment-resistant MD	3	1,2	Numbers
Nord, 2018	3-back>1-back, controls>MDD patients	15	1,3	Letters
Nord, 2018	3-back>1-back, relatives>MDD patients	6	1,3	Letters
Rodriguez-Cano, 2014	2-back>asterisk, controls>MDD	4	asterisk,2	Letters
Rodriguez-Cano, 2017	2-back>asterisk, controls>MDD	1	asterisk,2	Letters
Walsh, 2007	3,2,1>0-back, controls>MDD	2	0,1,2,3	Letters
Yüksel, 2018	2-back>0-back, controls>MDD patients	1	0,2	Letters
Yüksel, 2018	3-back>0-back, controls>MDD patients	2	0,3	Letters
Schizophrenia > Controls				
Bor, 2011	2-back>0-back, schizophrenia>controls	3	0,2	Letters and Dots (s)
Bor, 2011	2-back>0-back, schizophrenia>controls	1	0,2	Letters and Dots (v)
Becerril, 2010	2-back>fixation, schizophrenia>controls	6	fixation,2	Faces
Callicott, 2000	2>1>0-back, schizophrenia>controls	7	0,1,2	Numbers

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Callicott, 2003	2-back>0-back, schizophrenics>controls	7	0,2	Numbers
Ettinger, 2011	2,1,0 (group by load), schizophrenics>controls	2	0,1,2	Dots
Guerrero-Pedraza, 2012	2-back>asterisk, first episode psychosis>controls	2	asterisk,2	Letters
Guimond, 2018	2-back>0-back, schizophrenia patients>controls	1	0,2	Faces
Habel, 2010	2-back>0-back, male schizophrenics>controls	5	0,2	Letters
Jansma, 2003	3,2,1>0-back, schizophrenics (atypical)>controls	7	0,1,2,3*	Dots
Li, 2019	2-back>0-back, schizophrenia patients>controls	3	0,2	Symbols and Shapes
Madre, 2013	2>1>asterisk, schizo-affectives>controls	1	asterisk,1,2	Letters
Mendrek, 2004	2-back>0-back, schizophrenics>controls	6	0,2	Letters
Meyer-Lindenberg, 2001	2-back>0-back, schizophrenics>matched controls	4	0.2	Numbers
Nejad, 2011	2-back>1-back, first-episode SCZ>controls	6	1,2	Letters
Ortiz-Gil, 2011	2-back>1-back, schizophrenics>controls	2	1,2	Letters
Ortiz-Gil, 2011	2-back>asterisk, schizophrenics>controls	2	asterisk,2	Letters
Pomarol-Clotet, 2008	2-back>asterisk, chronic schizophrenia>controls	2	asterisk,2	Letters
Pomarol-Clotet, 2010	2-back>asterisk, schizophrenic patients>controls	2	asterisk,2	Letters
Royer, 2009	2-back>0-back, schizophrenia>controls	4	0,2	Letters
Sabri, 2003	2-back>0-back, chronic schizophrenia>controls	9	0,2	Numbers
Salgado-Pineda, 2018	2-back>1-back, chronic schizophrenia>controls	18	1,2	Letters
Salgado-Pineda, 2018	2-back>1-back, FEP schizophrenia>controls	6	1,2	Letters
Sapara, 2013	2-back>rest, schizophrenia>controls	5	rest,2	Dots
Sapara, 2013	2-back>1-back, schizophrenia>controls	3	1,2	Dots
Scheuerecker, 2008	2-back>0-back, schizophrenic inpatients>controls	1	0,2	Letters
Scheuerecker, 2008	2-back (d)>0-back (d), schizophrenia>controls	1	0d, 2d	Letters
Schneider, 2007	2-Back>0-back, schizophrenia>controls	3	0,2	Letters
Tan, 2006	2-back>1-back, schizophrenia>controls	2	1,2	Numbers
Thermenos, 2016	2-back>0-back, CHR for schizophrenia>controls	2	0,2	Letters
Walter, 2003	2-back>0-back, schizophrenia>controls	1	0,2	Letters
Yoo, 2005	2-back>0-back, schizophrenia>controls	2	0,2*	Faces
Schizophrenia < Controls				
Callicott, 2000	2>1>0-back, controls>schizophrenia	7	0,1,2	Numbers
Callicott, 2003	2-back>0-back, controls>schizophrenics	7	0,2	Numbers
Guimond, 2018	2-back>0-back, controls>schizophrenia patients	1	0,2	Faces
Habel, 2010	2-back>0-back, controls>male schizophrenics	6	0,2	Letters
Honey, 2003	2-back>0-back, controls>schizophrenic patients	2	0,2	Letters
Karch, 2009	2-back>0-back, controls>schizophrenic patients	13	0,2	Numbers
Kumari, 2006	2-back>0-back, controls>schizophrenia	1	0,2	Dots
Loeb, 2018	2-back>1-back, controls>COS	12	1,2	Letters
Loeb, 2018	2-back>1-back, siblings>COS	11	1,2	Letters
Madre, 2013	2>1>asterisk, controls> schizo-affectives	3	asterisk,1,2	Letters
Meisenzahl, 2006	2-back>0-back controls>schizophrenic inpatients	8	0,2	Letters
Mendrek, 2004	2-back>0-back, controls>schizophrenia	2	0,2	Letters
Meyer-Lindenberg, 2001	2-back>0-back, matched controls>schizophrenics	5	0,2	Numbers
Moser, 2018	2-back>0-back, schizophrenia>controls	6	0,2	Objects
Ortiz-Gil, 2011	2-back>asterisk, controls>schizophrenics	1	asterisk,2	Letters
Perlstein, 2001	GroupXload (0,1,2-back), controls>schizophrenia	1	0,1,2	Letters
Perlstein, 2003	GroupXload(0,1,2-back), controls>schizophrenia	1	0,1,2	Letters
Pomarol-Clotet, 2008	2-back>asterisk, controls>chronic schizophrenia	3	asterisk,2	Letters
Pomarol-Clotet, 2010	2-back>asterisk, controls>schizophrenic patients	3	asterisk,2	Letters
Salgado-Pineda, 2018	2-back>1-back, controls>chronic schizophrenia	36	1,2	Letters
Salgado-Pineda, 2018	2-back>1-back controls>FEP schizophrenia	12	1,2	Letters
Sapara, 2013	2-back>0-back, schizophrenia>controls	3	0,2	Dots
Scheuerecker, 2008	2-back>0-back, controls>schizophrenic inpatients	3	0,2	Letters
Scheuerecker, 2008	2-back (d)>0-back (d), controls>schizophrenia	1	0d,2d	Letters
Schneider, 2007	2-Back>0-back, controls>schizophrenia	2	0,2	Letters
Wykes, 2002	2-back>0-back, controls>schizophrenia	10	0,2	Letters
Yoo, 2005	2-back>0-back, controls> schizophrenia	15	0,2*	Faces

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TABLE 3. RESULTS

Condition/Cluster	Volume (mm^3)	Peak Coordinates (x, y, z)	Label	Brodmann area
Addiction				
Cluster 1	6728	37.5, 15.7, 40	Right MFG	6/9
Cluster 2	3672	-1.4, 21.5, 44.1	Left Cingulate Gyrus	8
Cluster 3	3648	-35.2, -53.2, 45.3	Left IPL	40/7
Cluster 4	2984	-25.7, 0.5, 50.2	Left MFG	6
Cluster 5	2848	40.5, -46.8, 41.6	Right IPL	40
ADHD				
Cluster 1	5976	-1.3, 21.1, 41	Left MFG	32/6
Cluster 2	3896	-41.2, 5.9, 30.3	Left precentral gyrus	9
Cluster 3	3504	37.6, -41, 39.6	Right IPL	40
Cluster 4	3296	38.6, 32.9, 27.8	Right MFG	9
Cluster 5	3096	-26.8, -60.9, -18.7	Left Declive	*
Bipolar Disorder				
Cluster 1	7000	-38.8, -48.7, 38.7	Left IPL	40
Cluster 2	6368	45.3, -44.5, 40.9	Right IPL	40
Cluster 3	3608	41.9, 32, 26.4	Right MFG	9
Cluster 4	3264	-1.1, 14.7, 46.1	Left Cingulate Gyrus	6
Cluster 5	3016	-40, 3.7, 29.9	Left Precentral Gyrus	6
Cluster 6	2848	34.5, 18, 1.1	Right Insula	47
Cluster 7	2536	48, 9.3, 24	Right IFG	9
Cluster 8	2352	27.9, 4.8 ,46.5	Right MFG	6
Controls				
Cluster 1	11976	-41.3, 8.2, 34.1	Left MFG	6
Cluster 2	11760	33.3, -55.8, 42.9	Right IPL	7/40
Cluster 3	11608	-36.5, -50.3, 41.4	Left IPL	40
Cluster 4	8400	0.1, 16.6, 45.1	Right MFG	6/32
Cluster 5	7152	45.2, 24.8, 26.3	Right MFG	9
Cluster 6	6424	-35, -65, -21	Left Declive	*
Cluster 7	5552	-4.8, -9.8, 11.5	Left Thalamus (MD)	*
Cluster 8	4560	30.8, 8.7, 51.6	Right MFG	6
Cluster 9	4448	-30.9, 19.1, 2.2	Left Insula	13
Cluster 10	4224	32.5, 19.4, -1	Right Insula	13/47
Cluster 11	3808	34.6, -62.6, -23	Right Declive	*
Depression				
Cluster 1	5496	41.1,- 48.4, 39.2	Right IPL	40
Cluster 2	3144	-35.1, -49.4, 38.2	Left IPL	40
Cluster 3	2920	1.1, 17.6, 43.3	Right Cingulate Gyrus	32
Psychopathologies				
Cluster 1	23424	38, 20.6, 32.1	Right MFG	6/9
Cluster 2	22176	-36.7, 11.1, 28.9	Left MFG	6/9
Cluster 3	14032	40.9,-47.1,41.1	Right IPL	40
Cluster 4	13144	-35.8, -50.4, 40.9	Left IPL	40
Cluster 5	10528	-0.3, 18.8, 43.4	Left MFG/Cingulate	6/32

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Cluster 6	5304	32.6, 20.1, 1.4	Right Insula	13
Cluster 7	4648	33.4, -62.7, -19.3	Right Cerebellar Declive	N/A
Cluster 8	4504	-15.2, -2.8, 9.7	Left Lentiform Nucleus	N/A
Cluster 9	4456	-30.5, -62.8, -21.2	Left Cerebellar Declive	N/A
Cluster 10	4392	-34.3, 49.6, 7.8	Left MFG	10
Schizophrenia				
Cluster 1	9448	40.4, -47.7, 42.5	Right IPL	40
Cluster 2	9424	-35.1, -51.2, 42	Left IPL	40
Cluster 3	8992	37.8, 5.9, 41.3	Right MFG	6
Cluster 4	5320	-45.8, 18.6, 25.3	Left MFG	9
Cluster 5	4344	-29.8, 5.5, 48.9	Left MFG	6
Cluster 6	3904	3.3, 19.6, 41.4	Right Cingulate Gyrus	32
Cluster 7	2952	40.7, 36.3, 26.7	Right MFG	9
Cluster 8	2936	34.4, 20.6, 6.2	Right Insula	13
Cluster 9	2784	-32.8, -61.7, -17	Left Declive	*
Cluster 10	2744	35.7, -60.7, -17.2	Right Declive	*
Controls > Addiction				
Cluster 1	2096	-35.3, -64.7, 37.2	Left Precuneus	39
Controls > ADHD				
Cluster 1	2416	39.6, 13.3, 34.8	Right MFG	9
Controls > Bipolar				
Cluster 1	2104	-32.5, -0.2, 48.3	Left MFG	6
Controls > Depression				
None				
Controls > Schizophrenia				
Cluster 1	2576	4.1, - 58.1, -16.9	Right Culmen	*
Cluster 2	2224	32.5, 23.4, -2.9	Right IFG	47
Addiction > Controls				
None				
ADHD > Controls				
None				
Bipolar > Controls				
Cluster 1	4112	-1.2, 38.3, -13.7	Left MFG	11
Depression > Controls				
None				
Schizophrenia > Controls				
Cluster 1	6000	-2, 32.3, -8.2	Left anterior cingulate	11/32
Psychopathologies > Controls				
Cluster 1	11720	-2, 34.2, -7.7	Left anterior cingulate	11/32
Controls > Psychopathologies				
Cluster 1	4480	5.2, -61, 46.5	Right Precuneus	7
Cluster 2	2928	33.5, 20.5, -2.8	Right Insula	13