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

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

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

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

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

particular, these regions (or region) may play a pivotal role in the pathophysiology of working-memory related deficits commonly observed in ADHD, addiction, bipolar disorder, depression and schizophrenia. Such a finding may suggest a novel target for treatment, a potential new way to predict the onset of mental illness, or a functional consequence resulting from the development of psychiatric illness.

METHODS

Criteria Selection for Data Used for Meta-Analysis. We conducted literature searches in both Google Scholar and PubMed utilizing the following terms alone and in combination: ‘n-back,’ ‘working memory,’ ‘2-back,’ and ‘3-back’. We constrained our results by keywords related to our psychopathologies of interest: ‘addiction,’ ‘nicotine,’ ‘cocaine,’ ‘marijuana,’ ‘ecstasy,’ ‘MDMA,’ ‘schizophrenia,’ ‘schizoaffective,’ ‘MDD,’ ‘depression,’ ‘bipolar,’ ‘mania,’ and ‘ADHD.’ Peer reviewed articles were also obtained using BrainMap’s Sleuth 3.0.3 software (17) employing the search procedure: Experiments → Paradigm Class → n-back and Subjects → Diagnosis → Alcoholism, Attention Deficit/ Hyperactivity Disorder, Bipolar Disorder, Depression, Major Depressive Disorder, Schizophrenia, and Substance Use Disorder. The obtained papers were further searched for citations of interest and authors were contacted directly if peak coordinates were missing from their reported analyses.

Studies were grouped into separate diagnostic categories determined by DSM-criteria at the time of their publication. This procedure resulted in the following five categories: Addiction, ADHD, Bipolar Disorder, MDD, and Schizophrenia. We used the DSM-V diagnostic criteria for classification purposes if a disorder was ambiguous. For example, Schizoaffective disorder was classified within the “Schizophrenia” category, as it fits within the DSM-V’s diagnostic category

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

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

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

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

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

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

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

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

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.

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.

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

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

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

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

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

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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.

REFERENCES

1. Rose EJ, Ebmeier KP. Pattern of impaired working memory during major depression. *Journal of Affective Disorders*. 2006 Feb 1;90(2):149–61.
2. Martinussen R, Hayden J, Hogg-johnson S, Tannock R. A Meta-Analysis of Working Memory Impairments in Children With Attention-Deficit/Hyperactivity Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2005 Apr 1;44(4):377–84.
3. Sabri O, Owega A, Schreckenberger M, Sturz L, Fimm B, Kunert P, et al. A Truly Simultaneous Combination of Functional Transcranial Doppler Sonography and H2150 PET Adds Fundamental New Information on Differences in Cognitive Activation Between Schizophrenics and Healthy Control Subjects. *J Nucl Med*. 2003 May 1;44(5):671–81.
4. Lee J, Park S. Working Memory Impairments in Schizophrenia: A Meta-Analysis. *Journal of Abnormal Psychology*. 2005;114(4):599–611.
5. Bechara A, Martin EM. Impaired Decision Making Related to Working Memory Deficits in Individuals With Substance Addictions. *Neuropsychology*. 2004;18(1):152–62.
7. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders. *AJP*. 2010 Jul 1;167(7):748–51.
8. Meisenzahl EM, Scheuerecker J, Zipse M, Ufer S, Wiesmann M, Frodl T, et al. Effects of treatment with the atypical neuroleptic quetiapine on working memory function: a functional MRI follow-up investigation. *Eur Arch Psychiatry Clin Neurosci*. 2006 Dec 1;256(8):522–31.
9. Bartova L, Meyer BM, Diers K, Rabl U, Scharinger C, Popovic A, et al. Reduced default mode network suppression during a working memory task in remitted major depression. *Journal of Psychiatric Research*. 2015 May 1;64:9–18.
10. Rodríguez-Cano E, Sarró S, Monté GC, Maristany T, Salvador R, McKenna PJ, et al. Evidence for structural and functional abnormality in the subgenual anterior cingulate cortex in major depressive disorder. *Psychological Medicine*. 2014 Nov;44(15):3263–73.
11. Laird AR, Fox PM, Price CJ, Glahn DC, Uecker AM, Lancaster JL, et al. ALE meta-analysis: Controlling the false discovery rate and performing statistical contrasts. *Human Brain Mapping*. 2005 May;25(1):155–64.
12. Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA. Meta-Analysis of the Functional Neuroanatomy of Single-Word Reading: Method and Validation. *NeuroImage*. 2002 Jul 1;16(3, Part A):765–80.
13. Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT. Coordinate-based ALE meta-analysis of neuroimaging data: A random-effects approach based on empirical estimates of spatial uncertainty. *Hum Brain Mapp*. 2009 Sep;30(9):2907–26.

14. Eickhoff SB, Bzdok D, Laird AR, Kurth F, Fox PT. Activation likelihood estimation meta-analysis revisited. *NeuroImage*. 2012 Feb 1;59(3):2349–61.
15. Poldrack RA, Baker CI, Durnez J, Gorgolewski KJ, Matthews PM, Munafò MR, et al. Scanning the horizon: towards transparent and reproducible neuroimaging research. *Nature Reviews Neuroscience*. 2017 Feb;18(2):115–26.
16. Kirchner WK. Age differences in short-term retention of rapidly changing information. *Journal of Experimental Psychology*. 1958;55(4):352–8.
17. Laird AR, Eickhoff SB, Fox PM, Uecker AM, Ray KL, Saenz JJ, et al. The BrainMap strategy for standardization, sharing, and meta-analysis of neuroimaging data. *BMC Research Notes*. 2011 Sep 9;4(1):349.
18. Tomasi D, Goldstein RZ, Telang F, Maloney T, Alia-Klein N, Caparelli EC, et al. Widespread disruption in brain activation patterns to a working memory task during cocaine abstinence. *Brain Research*. 2007 Sep 26;1171:83–92.
19. Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. 1988. New York: Theime. 1988;
20. Lacadie CM, Fulbright RK, Rajeevan N, Constable RT, Papademetris X. More accurate Talairach coordinates for neuroimaging using non-linear registration. *NeuroImage*. 2008 Aug 15;42(2):717–25.
21. Kochunov P, Lancaster J, Thompson P, Toga AW, Brewer P, Hardies J, et al. An Optimized Individual Target Brain in the Talairach Coordinate System. *NeuroImage*. 2002 Oct 1;17(2):922–7.
22. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Human Brain Mapping*. 2005;25(1):46–59.
23. Wang H, He W, Wu J, Zhang J, Jin Z, Li L. A coordinate-based meta-analysis of the n-back working memory paradigm using activation likelihood estimation. *Brain and Cognition*. 2019 Jun 1;132:1–12.
24. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *PNAS*. 2003 Jan 7;100(1):253–8.
25. Thomas Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*. 2011 Jun 8;106(3):1125–65.
26. Fletcher PC, Frith CD, Baker SC, Shallice T, Frackowiak RSJ, Dolan RJ. The Mind's Eye—Precuneus Activation in Memory-Related Imagery. *NeuroImage*. 1995 Sep 1;2(3):195–200.

27. Lundstrom BN, Ingvar M, Petersson KM. The role of precuneus and left inferior frontal cortex during source memory episodic retrieval. *NeuroImage*. 2005 Oct 1;27(4):824–34.
28. Wallentin M, Roepstorff A, Glover R, Burgess N. Parallel memory systems for talking about location and age in precuneus, caudate and Broca's region. *NeuroImage*. 2006 Oct 1;32(4):1850–64.
29. Frings L, Wagner K, Quiske A, Schwarzwald R, Spreer J, Halsband U, et al. Precuneus is involved in allocentric spatial location encoding and recognition. *Exp Brain Res*. 2006 Sep 1;173(4):661–72.
30. Jilka SR, Scott G, Ham T, Pickering A, Bonnelle V, Braga RM, et al. Damage to the Salience Network and Interactions with the Default Mode Network. *Journal of Neuroscience*. 2014 Aug 13;34(33):10798–807.
31. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control. *J Neurosci*. 2007 Feb 28;27(9):2349–56.
32. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct*. 2010 Jun 1;214(5):655–67.
33. Uddin LQ. Salience processing and insular cortical function and dysfunction. *Nat Rev Neurosci*. 2015 Jan;16(1):55–61.
34. Schneider B, Koenigs M. Human lesion studies of ventromedial prefrontal cortex. *Neuropsychologia*. 2017 Dec 1;107:84–93.
35. Jalbrzikowski M, Larsen B, Hallquist MN, Foran W, Calabro F, Luna B. Development of White Matter Microstructure and Intrinsic Functional Connectivity Between the Amygdala and Ventromedial Prefrontal Cortex: Associations With Anxiety and Depression. *Biological Psychiatry*. 2017 Oct 1;82(7):511–21.
36. Sun D, Gold AL, Swanson CA, Haswell CC, Brown VM, Stjepanovic D, et al. Threat-Induced Anxiety During Goal Pursuit Disrupts Amygdala-Prefrontal Cortex Connectivity in Posttraumatic Stress Disorder. *bioRxiv*. 2019 Apr 19;614446.
37. Potvin S, Lungu O, Lipp O, Lalonde P, Zaharieva V, Stip E, et al. Increased ventro-medial prefrontal activations in schizophrenia smokers during cigarette cravings. *Schizophrenia Research*. 2016 May 1;173(1):30–6.
38. Hiser J, Koenigs M. The Multifaceted Role of the Ventromedial Prefrontal Cortex in Emotion, Decision Making, Social Cognition, and Psychopathology. *Biological Psychiatry*. 2018 Apr 15;83(8):638–47.
39. Weilbacher RA, Gluth S. The Interplay of Hippocampus and Ventromedial Prefrontal Cortex in Memory-Based Decision Making. *Brain Sci* [Internet]. 2016 Dec 29 [cited 2020 Jan 2];7(1). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5297293/>

40. Hamm AG, Mattfeld AT. Distinct Neural Circuits Underlie Prospective and Concurrent Memory-Guided Behavior. *Cell Reports*. 2019 Sep 3;28(10):2541-2553.e4.
41. Longe O, Senior C, Rippon G. The Lateral and Ventromedial Prefrontal Cortex Work as a Dynamic Integrated System: Evidence from fMRI Connectivity Analysis. *Journal of Cognitive Neuroscience*. 2008 May 13;21(1):141–54.
42. Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, et al. Reciprocal Limbic-Cortical Function and Negative Mood: Converging PET Findings in Depression and Normal Sadness. *AJP*. 1999 May 1;156(5):675–82.
43. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proceedings of the National Academy of Sciences*. 2001 Jan 16;98(2):676–82.
44. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJS. Default-mode brain dysfunction in mental disorders: A systematic review. *Neuroscience & Biobehavioral Reviews*. 2009 Mar 1;33(3):279–96.
45. Sonuga-Barke EJS, Castellanos FX. Spontaneous attentional fluctuations in impaired states and pathological conditions: A neurobiological hypothesis. *Neuroscience & Biobehavioral Reviews*. 2007 Jan 1;31(7):977–86.
46. Whitfield-Gabrieli S, Thermenos HW, Milanovic S, Tsuang MT, Faraone SV, McCarley RW, et al. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *PNAS*. 2009 Jan 27;106(4):1279–84.
47. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends in Cognitive Sciences*. 2011 Oct 1;15(10):483–506.
48. Mayeli A, Misaki M, Zotev V, Tsuchiyagaito A, Zoubi OA, Phillips R, et al. Self-regulation of ventromedial prefrontal cortex activation using real-time fMRI neurofeedback—Influence of default mode network. *Human Brain Mapping*. 2020;41(2):342–52.
49. Barch DM, Sheline YI, Csernansky JG, Snyder AZ. Working memory and prefrontal cortex dysfunction: specificity to schizophrenia compared with major depression. *Biological Psychiatry*. 2003 Mar 1;53(5):376–84.
50. Becerril K, Barch D. Influence of Emotional Processing on Working Memory in Schizophrenia. *Schizophr Bull*. 2011 Sep 1;37(5):1027–38.
51. Bédard A-CV, Newcorn JH, Clerkin SM, Krone B, Fan J, Halperin JM, et al. Reduced Prefrontal Efficiency for Visuospatial Working Memory in Attention-Deficit/Hyperactivity Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2014 Sep 1;53(9):1020-1030.e6.

52. Bor J, Brunelin J, Sappey-Marinier D, Ibarrola D, d'Amato T, Suaud-Chagny M-F, et al. Thalamus abnormalities during working memory in schizophrenia. An fMRI study. *Schizophrenia Research*. 2011 Jan 1;125(1):49–53.
53. Brooks JO, Vizueta N, Penfold C, Townsend JD, Bookheimer SY, Altshuler LL. Prefrontal hypoactivation during working memory in bipolar II depression. *Psychological Medicine*. 2015 Jun;45(8):1731–40.
54. Bustamante J-C, Barrós-Loscertales A, Ventura-Campos N, Sanjuán A, Llopis J-J, Parcet M-A, et al. Right parietal hypoactivation in a cocaine-dependent group during a verbal working memory task. *Brain Research*. 2011 Feb 23;1375:111–9.
55. Callicott JH, Bertolino A, Mattay VS, Langheim FJP, Duyn J, Coppola R, et al. Physiological Dysfunction of the Dorsolateral Prefrontal Cortex in Schizophrenia Revisited. *Cereb Cortex*. 2000 Nov 1;10(11):1078–92.
56. Callicott JH, Mattay VS, Verchinski BA, Marengo S, Egan MF, Weinberger DR. Complexity of Prefrontal Cortical Dysfunction in Schizophrenia: More Than Up or Down. *AJP*. 2003 Dec 1;160(12):2209–15.
57. Campanella S, Peigneux P, Petit G, Lallemand F, Saeremans M, Noël X, et al. Increased Cortical Activity in Binge Drinkers during Working Memory Task: A Preliminary Assessment through a Functional Magnetic Resonance Imaging Study. *PLOS ONE*. 2013 Apr 25;8(4):e62260.
58. Chantiluke K, Barrett N, Giampietro V, Brammer M, Simmons A, Rubia K. Disorder-dissociated effects of fluoxetine on brain function of working memory in attention deficit hyperactivity disorder and autism spectrum disorder. *Psychological Medicine*. 2015 Apr;45(6):1195–205.
59. Relationship between working-memory network function and substance use: a 3-year longitudinal fMRI study in heavy cannabis users and controls - Cousijn - 2014 - *Addiction Biology* - Wiley Online Library [Internet]. [cited 2019 Oct 22]. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1111/adb.12111>
60. Cubillo A, Smith AB, Barrett N, Giampietro V, Brammer M, Simmons A, et al. Drug-specific laterality effects on frontal lobe activation of atomoxetine and methylphenidate in attention deficit hyperactivity disorder boys during working memory. *Psychological Medicine*. 2014 Feb;44(3):633–46.
61. Daumann J, Fimm B, Willmes K, Thron A, Gouzoulis-Mayfrank E. Cerebral activation in abstinent ecstasy (MDMA) users during a working memory task: a functional magnetic resonance imaging (fMRI) study. *Cognitive Brain Research*. 2003 May 1;16(3):479–87.
62. Deckersbach T, Rauch SL, Buhlmann U, Ostacher MJ, Beucke J-C, Nierenberg AA, et al. An fMRI investigation of working memory and sadness in females with bipolar disorder: a brief report. *Bipolar Disorders*. 2008;10(8):928–42.

63. Drapier D, Surguladze S, Marshall N, Schulze K, Fern A, Hall M-H, et al. Genetic Liability for Bipolar Disorder Is Characterized by Excess Frontal Activation in Response to a Working Memory Task. *Biological Psychiatry*. 2008 Sep 15;64(6):513–20.
64. Dumas JA, Newhouse PA. Impaired Working Memory in Geriatric Depression: An fMRI Study. *The American Journal of Geriatric Psychiatry*. 2015 Apr 1;23(4):433–6.
65. Ettinger U, Williams SCR, Fannon D, Premkumar P, Kuipers E, Möller H-J, et al. Functional magnetic resonance imaging of a parametric working memory task in schizophrenia: relationship with performance and effects of antipsychotic treatment. *Psychopharmacology*. 2011 Jul 1;216(1):17–27.
66. Fernández-Corcuera P, Salvador R, Monté GC, Salvador Sarró S, Goikolea JM, Amann B, et al. Bipolar depressed patients show both failure to activate and failure to de-activate during performance of a working memory task. *Journal of Affective Disorders*. 2013 Jun 1;148(2):170–8.
67. Fitzgerald PB, Srithiran A, Benitez J, Daskalakis ZZ, Oxley TJ, Kulkarni J, et al. An fMRI study of prefrontal brain activation during multiple tasks in patients with major depressive disorder. *Human Brain Mapping*. 2008;29(4):490–501.
68. Frangou S, Kington J, Raymont V, Shergill SS. Examining ventral and dorsal prefrontal function in bipolar disorder: A functional magnetic resonance imaging study. *European Psychiatry*. 2008 Jun 1;23(4):300–8.
69. Garrett A, Kelly R, Gomez R, Keller J, Schatzberg AF, Reiss AL. Aberrant Brain Activation During a Working Memory Task in Psychotic Major Depression. *AJP*. 2011 Feb 1;168(2):173–82.
70. Guerrero-Pedraza A, McKenna PJ, Gomar JJ, Sarró S, Salvador R, Amann B, et al. First-episode psychosis is characterized by failure of deactivation but not by hypo- or hyperfrontality. *Psychological Medicine*. 2012 Jan;42(1):73–84.
71. Haldane M, Jogia J, Cobb A, Kozuch E, Kumari V, Frangou S. Changes in brain activation during working memory and facial recognition tasks in patients with bipolar disorder with Lamotrigine monotherapy. *European Neuropsychopharmacology*. 2008 Jan 1;18(1):48–54.
72. Harvey P-O, Fossati P, Pochon J-B, Levy R, LeBastard G, Lehericy S, et al. Cognitive control and brain resources in major depression: An fMRI study using the n-back task. *NeuroImage*. 2005 Jul 1;26(3):860–9.
73. Honey GD, Bullmore ET, Soni W, Varatheesan M, Williams SCR, Sharma T. Differences in frontal cortical activation by a working memory task after substitution of risperidone for typical antipsychotic drugs in patients with schizophrenia. *Proceedings of the National Academy of Sciences*. 1999 Nov 9;96(23):13432–7.

74. Honey GD, Sharma T, Suckling J, Giampietro V, Soni W, Williams SCR, et al. The functional neuroanatomy of schizophrenic subsyndromes. *Psychological Medicine*. 2003 Sep;33(6):1007–18.
75. Honey GD, Bullmore ET, Sharma T. De-coupling of cognitive performance and cerebral functional response during working memory in schizophrenia. *Schizophrenia Research*. 2002 Jan 1;53(1):45–56.
76. Ionescu DF, Nugent AC, Luckenbaugh DA, Niciu MJ, Richards EM, Zarate CA, et al. Baseline working memory activation deficits in dimensional anxious depression as detected by magnetoencephalography. *Acta Neuropsychiatrica*. 2015 Jun;27(3):143–52.
77. Jansma JM, Ramsey NF, van der Wee NJA, Kahn RS. Working memory capacity in schizophrenia: a parametric fMRI study. *Schizophrenia Research*. 2004 Jun 1;68(2):159–71.
78. Jogia J, Dima D, Kumari V, Frangou S. Frontopolar cortical inefficiency may underpin reward and working memory dysfunction in bipolar disorder. *The World Journal of Biological Psychiatry*. 2012 Dec 1;13(8):605–15.
79. Karch S, Leicht G, Giegling I, Lutz J, Kunz J, Buselmeier M, et al. Inefficient neural activity in patients with schizophrenia and nonpsychotic relatives of schizophrenic patients: Evidence from a working memory task. *Journal of Psychiatric Research*. 2009 Oct 1;43(15):1185–94.
80. Kim J-J, Kwon JS, Park HJ, Youn T, Kang DH, Kim MS, et al. Functional Disconnection Between the Prefrontal and Parietal Cortices During Working Memory Processing in Schizophrenia: A [¹⁵O]H₂O PET Study. *AJP*. 2003 May 1;160(5):919–23.
81. Kumari V, Aasen I, Taylor P, ffytche DH, Das M, Barkataki I, et al. Neural dysfunction and violence in schizophrenia: An fMRI investigation. *Schizophrenia Research*. 2006 May 1;84(1):144–64.
82. Li Y, Li F, He N, Guo L, Huang X, Lui S, et al. Neural hyperactivity related to working memory in drug-naïve boys with attention deficit hyperactivity disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2014 Aug 4;53:116–22.
83. Loughhead J, Wileyto EP, Ruparel K, Falcone M, Hopson R, Gur R, et al. Working Memory-Related Neural Activity Predicts Future Smoking Relapse. *Neuropsychopharmacol*. 2015 May;40(6):1311–20.
84. Marquand AF, Mourão-Miranda J, Brammer MJ, Cleare AJ, Fu CHY. Neuroanatomy of verbal working memory as a diagnostic biomarker for depression. *NeuroReport*. 2008 Oct 8;19(15):1507.
85. Massat I, Slama H, Kavec M, Linotte S, Mary A, Baleriaux D, et al. Working Memory-Related Functional Brain Patterns in Never Medicated Children with ADHD. *PLOS ONE*. 2012 Nov 14;7(11):e49392.

86. Matsuo K, Glahn DC, Peluso M a. M, Hatch JP, Monkul ES, Najt P, et al. Prefrontal hyperactivation during working memory task in untreated individuals with major depressive disorder. *Mol Psychiatry*. 2007 Feb;12(2):158–66.
87. Mattfeld AT, Whitfield-Gabrieli S, Biederman J, Spencer T, Brown A, Fried R, et al. Dissociation of working memory impairments and attention-deficit/hyperactivity disorder in the brain. *NeuroImage: Clinical*. 2016 Jan 1;10:274–82.
88. McClernon FJ, Froeliger B, Rose JE, Kozink RV, Addicott MA, Sweitzer MM, et al. The effects of nicotine and non-nicotine smoking factors on working memory and associated brain function. *Addiction Biology*. 2016;21(4):954–61.
89. Mendrek A, Kiehl KA, Smith AM, Irwin D, Forster BB, Liddle PF. Dysfunction of a distributed neural circuitry in schizophrenia patients during a working-memory performance. *Psychological Medicine*. 2005 Feb;35(2):187–96.
90. Meusel L-AC, Hall GBC, Fougere P, McKinnon MC, MacQueen GM. Neural correlates of cognitive remediation in patients with mood disorders. *Psychiatry Research: Neuroimaging*. 2013 Nov 30;214(2):142–52.
91. Monks PJ, Thompson JM, Bullmore ET, Suckling J, Brammer MJ, Williams SC, et al. A functional MRI study of working memory task in euthymic bipolar disorder: evidence for task-specific dysfunction. *Bipolar Disorders*. 2004;6(6):550–64.
92. Nejad AB, Ebdrup BH, Siebner HR, Rasmussen H, Aggernæs B, Glenthøj BY, et al. Impaired temporoparietal deactivation with working memory load in antipsychotic-naïve patients with first-episode schizophrenia. *The World Journal of Biological Psychiatry*. 2011 Jun 1;12(4):271–81.
93. Nichols TT, Gates KM, Molenaar PCM, Wilson SJ. Greater BOLD activity but more efficient connectivity is associated with better cognitive performance within a sample of nicotine-deprived smokers. *Addiction Biology*. 2014;19(5):931–40.
94. Norbury R, Godlewska B, Cowen PJ. When less is more: a functional magnetic resonance imaging study of verbal working memory in remitted depressed patients. *Psychological Medicine*. 2014 Apr;44(6):1197–203.
95. Ortiz-Gil J, Pomarol-Clotet E, Salvador R, Canales-Rodríguez EJ, Sarró S, Gomar JJ, et al. Neural correlates of cognitive impairment in schizophrenia. *The British Journal of Psychiatry*. 2011 Sep;199(3):202–10.
96. Padula CB, Schweinsburg AD, Tapert SF. Spatial working memory performance and fMRI activation interaction in abstinent adolescent marijuana users. *Psychology of Addictive Behaviors*. 2007;21(4):478–87.
97. Perlstein WM, Carter CS, Noll DC, Cohen JD. Relation of Prefrontal Cortex Dysfunction to Working Memory and Symptoms in Schizophrenia. *AJP*. 2001 Jul 1;158(7):1105–13.

98. Perlstein WM, Dixit NK, Carter CS, Noll DC, Cohen JD. Prefrontal cortex dysfunction mediates deficits in working memory and prepotent responding in schizophrenia. *Biological Psychiatry*. 2003 Jan 1;53(1):25–38.
99. Pfefferbaum A, Desmond JE, Galloway C, Menon V, Glover GH, Sullivan EV. Reorganization of Frontal Systems Used by Alcoholics for Spatial Working Memory: An fMRI Study. *NeuroImage*. 2001 Jul 1;14(1):7–20.
100. Pomarol-Clotet E, Canales-Rodríguez EJ, Salvador R, Sarró S, Gomar JJ, Vila F, et al. Medial prefrontal cortex pathology in schizophrenia as revealed by convergent findings from multimodal imaging. *Molecular Psychiatry*. 2010 Aug;15(8):823–30.
101. Pomarol-Clotet E, Salvador R, Sarró S, Gomar J, Vila F, Martínez Á, et al. Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network? *Psychological Medicine*. 2008 Aug;38(8):1185–93.
102. Pomarol-Clotet E, Alonso-Lana S, Moro N, Sarró S, Bonnin MC, Goikolea JM, et al. Brain functional changes across the different phases of bipolar disorder. *The British Journal of Psychiatry*. 2015 Feb;206(2):136–44.
103. Pomarol-Clotet E, Moro N, Sarró S, Goikolea JM, Vieta E, Amann B, et al. Failure of deactivation in the medial frontal cortex in mania: evidence for default mode network dysfunction in the disorder. *The World Journal of Biological Psychiatry*. 2012 Dec 1;13(8):616–26.
104. Rose EJ, Simonotto E, Ebmeier KP. Limbic over-activity in depression during preserved performance on the n-back task. *NeuroImage*. 2006 Jan 1;29(1):203–15.
105. Royer A, Schneider FCG, Grosselin A, Pellet J, Barral F-G, Laurent B, et al. Brain activation during executive processes in schizophrenia. *Psychiatry Research: Neuroimaging*. 2009 Sep 30;173(3):170–6.
106. Sapara A, ffytche DH, Birchwood M, Cooke MA, Fannon D, Williams SCR, et al. Preservation and compensation: The functional neuroanatomy of insight and working memory in schizophrenia. *Schizophrenia Research*. 2014 Jan 1;152(1):201–9.
107. Scheuerecker J, Ufer S, Zipse M, Frodl T, Koutsouleris N, Zetzsche T, et al. Cerebral changes and cognitive dysfunctions in medication-free schizophrenia – An fMRI study. *Journal of Psychiatric Research*. 2008 May 1;42(6):469–76.
108. Schneider F, Habel U, Reske M, Kellermann T, Stöcker T, Shah NJ, et al. Neural correlates of working memory dysfunction in first-episode schizophrenia patients: An fMRI multi-center study. *Schizophrenia Research*. 2007 Jan 1;89(1):198–210.
109. Schöning S, Zwitterlood P, Engelien A, Behnken A, Kugel H, Schifffbauer H, et al. Working-memory fMRI reveals cingulate hyperactivation in euthymic major depression. *Human Brain Mapping*. 2009;30(9):2746–56.

110. Schweinsburg AD, Schweinsburg BC, Medina KL, McQueeney T, Brown SA, Tapert SF. The Influence of Recency of Use on fMRI Response During Spatial Working Memory in Adolescent Marijuana Users. *Journal of Psychoactive Drugs*. 2010 Sep 1;42(3):401–12.
111. Smith AM, Longo CA, Fried PA, Hogan MJ, Cameron I. Effects of marijuana on visuospatial working memory: an fMRI study in young adults. *Psychopharmacology*. 2010 Jun;210(3):429–38.
112. Surguladze SA, Chu EM, Evans A, Anilkumar APP, Patel MX, Timehin C, et al. The Effect of Long-Acting Risperidone on Working Memory in Schizophrenia: A Functional Magnetic Resonance Imaging Study. *Journal of Clinical Psychopharmacology*. 2007 Dec;27(6):560.
113. Sweet LH, Mulligan RC, Finnerty CE, Jerskey BA, David SP, Cohen RA, et al. Effects of nicotine withdrawal on verbal working memory and associated brain response. *Psychiatry Research: Neuroimaging*. 2010 Jul 30;183(1):69–74.
114. Tan H-Y, Sust S, Buckholtz JW, Mattay VS, Meyer-Lindenberg A, Egan MF, et al. Dysfunctional Prefrontal Regional Specialization and Compensation in Schizophrenia. *AJP*. 2006 Nov 1;163(11):1969–77.
115. Thermenos HW, Goldstein JM, Milanovic SM, Whitfield-Gabrieli S, Makris N, LaViolette P, et al. An fMRI study of working memory in persons with bipolar disorder or at genetic risk for bipolar disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*. 2010;153B(1):120–31.
116. Townsend J, Bookheimer SY, Foland-Ross LC, Sugar CA, Altshuler LL. fMRI abnormalities in dorsolateral prefrontal cortex during a working memory task in manic, euthymic and depressed bipolar subjects. *Psychiatry Research: Neuroimaging*. 2010 Apr 30;182(1):22–9.
117. Valera EM, Brown A, Biederman J, Faraone SV, Makris N, Monuteaux MC, et al. Sex Differences in the Functional Neuroanatomy of Working Memory in Adults With ADHD. *AJP*. 2010 Jan 1;167(1):86–94.
118. Valera EM, Faraone SV, Biederman J, Poldrack RA, Seidman LJ. Functional neuroanatomy of working memory in adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry*. 2005 Mar 1;57(5):439–47.
119. Walsh ND, Williams SCR, Brammer MJ, Bullmore ET, Kim J, Suckling J, et al. A Longitudinal Functional Magnetic Resonance Imaging Study of Verbal Working Memory in Depression After Antidepressant Therapy. *Biological Psychiatry*. 2007 Dec 1;62(11):1236–43.
120. Walter H, Wunderlich AP, Blankenhorn M, Schäfer S, Tomczak R, Spitzer M, et al. No hypofrontality, but absence of prefrontal lateralization comparing verbal and spatial working memory in schizophrenia. *Schizophrenia Research*. 2003 Jun 1;61(2):175–84.

121. Wykes T, Brammer M, Mellers J, Bray P, Reeder C, Williams C, et al. Effects on the brain of a psychological treatment: Cognitive remediation therapy: Functional magnetic resonance imaging in schizophrenia. *The British Journal of Psychiatry*. 2002 Aug;181(2):144–52.
122. Xu J, Mendrek A, Cohen MS, Monterosso J, Rodriguez P, Simon SL, et al. Brain Activity in Cigarette Smokers Performing a Working Memory Task: Effect of Smoking Abstinence. *Biological Psychiatry*. 2005 Jul 15;58(2):143–50.
123. Owens MM, McNally S, Petker T, Amlung MT, Balodis IM, Sweet LH, et al. Urinary tetrahydrocannabinol is associated with poorer working memory performance and alterations in associated brain activity. *Neuropsychopharmacology*. 2019 Feb;44(3):613–9.
124. Sirnes E, Griffiths ST, Aukland SM, Eide GE, Elgen IB, Gundersen H. Functional MRI in prenatally opioid-exposed children during a working memory-selective attention task. *Neurotoxicology and Teratology*. 2018 Mar;66:46–54.
125. Wesley MJ, Lile JA, Fillmore MT, Porrino LJ. Neurophysiological capacity in a working memory task differentiates dependent from nondependent heavy drinkers and controls. *Drug and Alcohol Dependence*. 2017 Jun;175:24–35.
126. Ko C-H, Hsieh T-J, Wang P-W, Lin W-C, Chen C-S, Yen J-Y. The Altered Brain Activation of Phonological Working Memory, Dual Tasking, and Distraction Among Participants With Adult ADHD and the Effect of the MAOA Polymorphism. *Journal of Attention Disorders*. 2018 Feb;22(3):240–9.
127. Macoveanu J, Demant KM, Vinberg M, Siebner HR, Kessing LV, Miskowiak KW. Towards a biomarker model for cognitive improvement: No change in memory-related prefrontal engagement following a negative cognitive remediation trial in bipolar disorder. *Journal of Psychopharmacology*. 2018 Oct;32(10):1075–85.
128. Miskowiak K, Kjaerstad H, Støttrup M, Svendsen A, Demant K, Hoeffding L, et al. The catechol-O-methyltransferase (*COMT*) Val158Met genotype modulates working memory-related dorsolateral prefrontal response and performance in bipolar disorder. *Bipolar Disorders*. 2017 May;19(3):214–24.
129. Rodríguez-Cano E, Alonso-Lana S, Sarró S, Fernández-Corcuera P, Goikolea JM, Vieta E, et al. Differential failure to deactivate the default mode network in unipolar and bipolar depression. *Bipolar Disorders*. 2017 Aug;19(5):386–95.
130. Miskowiak KW, Vinberg M, Glerup L, Paulson OB, Knudsen GM, Ehrenreich H, et al. Neural correlates of improved executive function following erythropoietin treatment in mood disorders. *Psychological Medicine*. 2016 Jun;46(8):1679–91.
131. Rodríguez-Cano E, Alonso-Lana S, Sarró S, Fernández-Corcuera P, Goikolea JM, Vieta E, et al. Differential failure to deactivate the default mode network in unipolar and bipolar depression. *Bipolar Disorders*. 2017 Aug;19(5):386–95.

132. Guimond S, Padani S, Lutz O, Eack S, Thermenos H, Keshavan M. Impaired regulation of emotional distractors during working memory load in schizophrenia. *Journal of Psychiatric Research*. 2018 Jun;101:14–20.
133. Li X, Yi Z, Lv Q, Chu M, Hu H, Wang J, et al. Clinical utility of the dual n-back task in schizophrenia: A functional imaging approach. *Psychiatry Research: Neuroimaging*. 2019 Feb;284:37–44.
134. Charlet K, Beck A, Jorde A, Wimmer L, Vollstädt-Klein S, Gallinat J, et al. Increased neural activity during high working memory load predicts low relapse risk in alcohol dependence. *Addiction Biology*. 2014;19(3):402–14.
135. Ko C-H, Yen J-Y, Yen C-F, Chen C-S, Lin W-C, Wang P-W, et al. Brain activation deficit in increased-load working memory tasks among adults with ADHD using fMRI. *Eur Arch Psychiatry Clin Neurosci*. 2013 Oct 1;263(7):561–73.
136. Salavert J, Ramos-Quiroga JA, Moreno-Alcázar A, Caseras X, Palomar G, Radua J, et al. Functional Imaging Changes in the Medial Prefrontal Cortex in Adult ADHD. *J Atten Disord*. 2018 May 1;22(7):679–93.
137. Madre M, Pomarol-Clotet E, McKenna P, Radua J, Ortiz-Gil J, Panicali F, et al. Brain functional abnormality in schizo-affective disorder: an fMRI study. *Psychological Medicine*. 2013 Jan;43(1):143–53.
138. YOO S-S, CHOI B-G, JUH R-H, PARK J-M, PAE C-U, KIM J-J, et al. WORKING MEMORY PROCESSING OF FACIAL IMAGES IN SCHIZOPHRENIA: fMRI INVESTIGATION. *International Journal of Neuroscience*. 2005 Jan 1;115(3):351–66.
139. Daumann Jörg, Fischermann T, Heekeren K, Thron A, Gouzoulis-Mayfrank E. Neural mechanisms of working memory in ecstasy (MDMA) users who continue or discontinue ecstasy and amphetamine use: Evidence from an 18-month longitudinal functional magnetic resonance imaging study. *Biological Psychiatry*. 2004 Sep 1;56(5):349–55.
140. Livny A, Cohen K, Tik N, Tsarfaty G, Rosca P, Weinstein A. The effects of synthetic cannabinoids (SCs) on brain structure and function. *European Neuropsychopharmacology*. 2018 Sep 1;28(9):1047–57.
141. Bayerl M, Dielentheis TF, Vucurevic G, Gesierich T, Vogel F, Fehr C, et al. Disturbed brain activation during a working memory task in drug-naive adult patients with ADHD. *NeuroReport*. 2010 Apr 21;21(6):442.
142. Brown A, Biederman J, Valera E, Lomedico A, Aleardi M, Makris N, et al. Working memory network alterations and associated symptoms in adults with ADHD and Bipolar Disorder. *Journal of Psychiatric Research*. 2012 Apr 1;46(4):476–83.
143. Kobel M, Bechtel N, Weber P, Specht K, Klarhöfer M, Scheffler K, et al. Effects of methylphenidate on working memory functioning in children with attention

860 deficit/hyperactivity disorder. *European Journal of Paediatric Neurology*. 2009 Nov
861 1;13(6):516–23.

862 144. Alonso-Lana S, Valentí M, Romaguera A, Sarri C, Sarró S, Rodríguez-Martínez A, et al.
863 Brain functional changes in first-degree relatives of patients with bipolar disorder: evidence
864 for default mode network dysfunction. *Psychological Medicine*. 2016 Sep;46(12):2513–21.

865 145. Alonso-Lana S, Moro N, McKenna PJ, Sarró S, Romaguera A, Monté GC, et al.
866 Longitudinal brain functional changes between mania and euthymia in bipolar disorder.
867 *Bipolar Disorders*. 2019;21(5):449–57.

868 146. Dima D, Roberts RE, Frangou S. Connectomic markers of disease expression, genetic risk
869 and resilience in bipolar disorder. *Transl Psychiatry*. 2016 Jan;6(1):e706–e706.

870 147. Moser DA, Doucet GE, Lee WH, Rasgon A, Krinsky H, Leibu E, et al. Multivariate
871 Associations Among Behavioral, Clinical, and Multimodal Imaging Phenotypes in Patients
872 With Psychosis. *JAMA Psychiatry*. 2018 Apr 1;75(4):386–95.

873 148. Nord C, Halahakoon DC, Lally N, Limbachya T, Pilling S, Roiser J. Dorsolateral Prefrontal
874 Cortex Activity is Impaired in Currently-Depressed Patients, But Intact in Individuals at
875 High Risk: A Three-Group Functional MRI Study of Hot and Cold Cognition [Internet].
876 Rochester, NY: Social Science Research Network; 2018 Jun [cited 2020 Jan 3]. Report No.:
877 ID 3204760. Available from: <https://papers.ssrn.com/abstract=3204760>

878 149. Yüksel D, Dietsche B, Konrad C, Dannlowski U, Kircher T, Krug A. Neural correlates of
879 working memory in first episode and recurrent depression: An fMRI study. *Progress in*
880 *Neuro-Psychopharmacology and Biological Psychiatry*. 2018 Jun 8;84:39–49.

881 150. Frangou S, Dima D, Jogia J. Towards person-centered neuroimaging markers for resilience
882 and vulnerability in Bipolar Disorder. *NeuroImage*. 2017 Jan 15;145:230–7.

883 151. Habel U, Pauly K, Koch K, Kellermann T, Reske M, Backes V, et al. Emotion–cognition
884 interactions in schizophrenia. *The World Journal of Biological Psychiatry*. 2010 Dec
885 1;11(8):934–44.

886 152. Meyer-Lindenberg A, Poline J-B, Kohn PD, Holt JL, Egan MF, Weinberger DR, et al.
887 Evidence for Abnormal Cortical Functional Connectivity During Working Memory in
888 Schizophrenia. *AJP*. 2001 Nov 1;158(11):1809–17.

889 153. Salgado-Pineda P, Radua J, Sarró S, Guerrero-Pedraza A, Salvador R, Pomarol-Clotet E, et
890 al. Sensitivity and specificity of hypoactivations and failure of de-activation in
891 schizophrenia. *Schizophrenia Research*. 2018 Nov 1;201:224–30.

892 154. Loeb FF, Zhou X, Craddock KES, Shora L, Broadnax DD, Gochman P, et al. Reduced
893 Functional Brain Activation and Connectivity During a Working Memory Task in
894 Childhood-Onset Schizophrenia. *Journal of the American Academy of Child & Adolescent*
895 *Psychiatry*. 2018 Mar 1;57(3):166–74.

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.

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 than healthy controls (red). The latter contrast converges in IACC/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.

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.

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.

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

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

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

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

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

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

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

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

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