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# Mapping working memory-specific dysfunction using a transdiagnostic approach

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ABSTRACT

*Background:* Working memory (WM) is an executive ability that allows one to hold and manipulate information for a short period of time. Schizophrenia and mood disorders are severe psychiatric conditions with overlapping genetic and clinical symptoms. Whilst WM has been suggested as meeting the criteria for being an *endophenotype* for schizophrenia and mood disorders, it still unclear whether they share overlapping neural circuitry.
*Objective:* The n-back task has been widely used to measure WM capacity, such as maintenance, flexible updating, and interference control. Here we compiled studies that included psychiatric populations, i.e., schizophrenia, bipolar disorder and major depressive disorder.
*Methods:* We performed a coordinate-based *meta*-analysis that combined 34 BOLD-fMRI studies comparing activity associated with n-back working memory between psychiatric patients and healthy controls. We specifically focused our search using the n-back task to diminish study heterogeneity.
*Results:* All patient groups showed blunted activity in the striatum, anterior insula and frontal lobe. The same brain networks related to WM were compromised in schizophrenia, major depressive disorder and bipolar disorder.
*Conclusion:* Our findings support the suggestion of commonal functional abnormalities across schizophrenia and mood disorders related to WM.

## 1. Introduction

Psychiatric disorders are complex debilitating conditions characterized by anhedonia, delusions, and cognitive impairments (Purcell et al., 2009). Although working memory has long been considered a prominent cognitive impairment in neuropsychiatric disorders, especially schizophrenia and mood disorders, its underlying neurobiological mechanisms remain poorly understood. Notably, schizophrenia and mood disorders have been reported to share similar overlapping genetic and clinical symptoms (see research topic published by Misiak et al., 2016; Brandt et al., 2014). This preliminary observation led to the concept of *endophenotype* which refers to a measurable construct that allows one to bridge the gap between phenotype and genetic variability (Gottesman and Gould, 2003). Furthermore, a number of genetic (William et al., 2011; Lee et al. 2012), cognitive (Hill et al., 2008; Vöhringer et al., 2013; Sitskoorn et al., 2004; Balanzá-Martínez et al., 2008; Glahn et al., 2010), and neuroimaging studies (Brandt et al., 2014) provided a broader understanding into the overlapping nature of schizophrenia and mood disorders. For example, patients with schizophrenia and bipolar disorder share high levels of schizotypy, which possesses high heritability and co-segregation (Grant, 2015). With regards to the literature in genetics, it has been proposed that phospholipase C-β1 (PLC-β1) hypofunctionality is associated with schizophrenia and bipolar disorder (Yang et al., 2016). Further cognitive impairments, such as working memory, has been reported in both disorders (Green, 2006; Simonsen et al., 2011), attributing to an endophenotype. However, to our knowledge, no previous *meta*-analysis has provided compelling and robust evidence of whether these disorders

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shared common putative brain regions related to working memory activities. Notably, the NIMH Research Domain Criteria (RDoC) project is seeking to use the fundamental cognitive dimensions of functioning to identify specific transdiagnostic neural markers of working memory (Insel et al., 2010).

Working memory is a multidimensional construct that allows one to hold and manipulate information in mind for a short period of time while suppressing irrelevant information (Baddeley and Hitch, 1974). The most commonly used working memory paradigm is the n-back task (Kirchner, 1958), which has been used by cognitive neuroscientists since the mid-1990 s. Due to the popularity of the n-back task in cognitive neuroscience (Callicott et al., 1999; Corbetta and Shulman, 2002; Naghavi and Nyberg, 2005; Spreng et al., 2010), many studies have been made available, yielding the first functional magnetic resonance imaging (fMRI) *meta*-analysis in 2005 by Owen and colleagues. Results from this neuroimaging *meta*-analysis revealed a consistent set of brain areas engaged during performance of the n-back task, including the prefrontal and parietal cortices yet also ventral medial prefrontal cortex, bilateral insula, and premotor cortex (Owen et al., 2005). More recently, a series of *meta*-analyses examining brain responses across the lifespan revealing similar regions yet lacking prefrontal concordant activation for young (Yaple and Arsalidou, 2018) and older ages (Yaple et al., 2019).

With regards to working memory processing in psychiatric populations, a number of fMRI *meta*-analyses have been performed on schizophrenia/psychosis (e.g., Glahn et al., 2005; Ragland et al., 2009; Li et al., 2015; Del Casale et al., 2016; Zhang et al., 2016) and major depressive disorder (Wang et al., 2015). The literature on working memory in mood disorders reveals inconsistent findings across studies. Inconsistencies reported among these studies have been attributed to differences in working memory load; i.e. frontal activity is reduced or enhanced depending on the allocation of attention that one allocates to the tasks. For example, one study reported hypoactivation of the prefrontal lobe in bipolar disorder (Brooks et al., 2015), studies focusing on major depressive disorder have revealed hypoactivation of the striatum (Hammar et al., 2016) as well as the dorsolateral prefrontal cortex (Brody et al., 2001; Rogers et al., 2004; Dichter et al., 2009). A recent review article gathered studies comparing neural activation between healthy controls and bipolar disorder patients (Cremaschi et al., 2013).

Here, we aim to perform a series of *meta*-analyses using the fMRI activation likelihood estimation (ALE) *meta*-analysis method. Notably, most of the previous studies performed *meta*-analyses using coordinates from between-group differences (e.g., Ragland et al., 2009; Schwindt and Black, 2009; Browndyke et al., 2013; Wang et al., 2015; Del Casale et al., 2016; Zhang et al., 2016). A caveat of using between-group contrasts (e.g., schizophrenia > healthy controls) as opposed to using process-related contrasts (e.g. 2 > 0 back) within each group is that the former method omits brain regions common in both clinical and healthy groups. Moreover, many of the abovementioned *meta*-analyses report too few studies (Glahn et al., 2005; Li et al., 2015; Wang et al., 2016) which leads to the reduced power of the *meta*-analysis software GingerALE requiring a minimum sample of 17 experiments to reach satisfactory statistical power (Eickhoff et al., 2017). A third disadvantage to the prior *meta*-analysis studies is that all but one (Glahn et al., 2005) used a variety of tasks to investigate various memory processes which may confound the results by increasing study heterogeneity, a common issue with the *meta*-analysis approach (Singh et al., 2017). Therefore, we aimed to perform within-group ALE *meta*-analyses to provide a context for interpreting the working memory-related contrast and conjunction related differences. In the contrast and conjunction analyses, the transdiagnostic ALE analysis of the literature on schizophrenia, major depression disorder and bipolar disorder was examined to provide an integrated framework of the neural basis of working memory. Later, the analysis focused specifically on schizophrenia, mood disorder and bipolar disorder was used to dissociate the specific working memory-related neurobiological impairments from potential disease general impairments. This transdiagnostic approach has the potential to identify the specific neurobiological framework for certain clinical symptoms and cognitive impairments across different disease stages and potentially improve tailored treatment strategies. In addition, we also compared these clinical groups with healthy controls to understand which regions were likely to succumb to decrease or increase activity, which may inform prior between-subjects *meta*-analysis reports (Ragland et al., 2009; Schwindt and Black, 2009; Browndyke et al., 2013; Wang et al., 2015; Del Casale et al., 2016; Zhang et al., 2016). Reported variability of hypo- and hyperactivation of the frontal lobe in schizophrenia patients has been hypothesized as dependant on the level of working memory load (Callicott et al., 2000, 2003; Barch, 2005). Consequently, we also aim to perform additional *meta*-analyses on schizophrenia patients and healthy participants, specifically focusing on the 2 > 0 back contrast.

## 2. Methods

### 2.1. Literature search and article selection

Eligible articles were identified by searching in the Web of Science database (http://www.webofknowledge.com) on 8th April 2019 with the following key terms: [fMRI AND n-back AND disorder OR schizophrenia OR "mild cognitive impairment" OR depression OR Alzheimer OR "attention deficit" OR bipolar OR anxiety OR obsessive–compulsive OR autism OR "personality disorder" OR gambling. After removing duplicates, a total of 343 articles were screened. Fig. 1 shows the yield of the searches and the steps taken to screen and identify eligible articles. Specifically, articles that used the n-back task with fMRI and reported whole-brain, random-effects results of within-group experiments (i.e., contrasts) in patients were included in the *meta*-analysis. Coordinates needed to be reported either in Talairach or Montreal Neurology Institute (MNI) coordinate space. The final dataset contained at least 17 contrasts for the following clinical populations: bipolar disorder, major depressive disorder and schizophrenia. Throughout the following report, we will focus only on these clinical groups.

### 2.2. Software tools

GingerALE is a freely available, quantitative *meta*-analysis method first proposed by Turkeltaub et al. (2002), with the latest version described by Eickhoff and colleagues (2009; 2017) and Turkeltaub and colleagues (2012). GingerALE, version 2.3.6 was used (http://brainmap.org/ale/), which relies on activation likelihood estimation (ALE) to compare coordinates compiled from multiple articles and which estimates the magnitude of overlap, yielding clusters most likely to become active across studies. The most recent algorithm minimizes within-group effects and provides increased power by allowing for the inclusion of all possible relevant experiments (Turkeltaub et al., 2012; Eickhoff et al., 2017). All coordinates were transformed into a common atlas space: Talairach coordinates were converted to MNI using the Lancaster et al. (2007) transformation algorithm. Resulting statistical maps were thresholded at $p < 0.05$ using a cluster-level correction for multiple comparisons and a cluster forming threshold at $p < 0.001$ (Eickhoff et al., 2017).

Analyses contrasting the clinical populations were calculated. Tests for differences and conjunction analysis were used to examine results for ALE maps associated with n-back performance between groups. The threshold for group-contrasts was set to $p < 0.01$ uncorrected for multiple comparisons (5000 permutations, 50 $mm^3$ minimum cluster-size; e.g., Sokolowski et al., 2017; Arsalidou et al., 2018) because group-contrast analyses use cluster-level thresholded ALE maps for each group, which have already been controlled for multiple comparisons.

### 2.3. Analyses

Four *meta*-analyses were performed and compared using GingerALE:

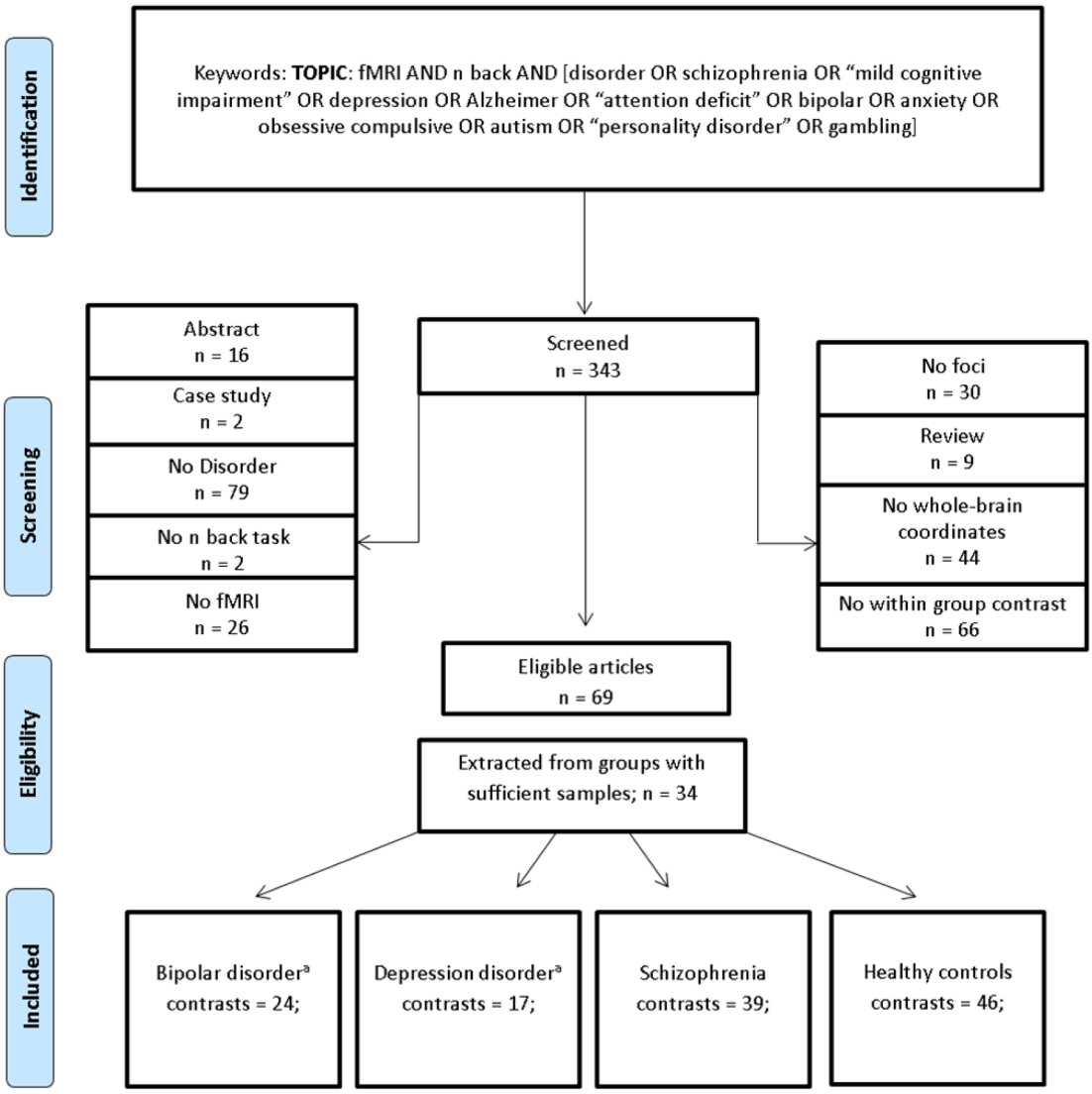


**Fig. 1.** Fig. 1. PRISMA flowchart for eligibility; a = two studies included in bipolar and depression *meta*-analyses (Miskowiak et al, 2016; Rodríguez-Cano et al., 2016).

(a) bipolar disorder (24 contrasts), (b) major depressive disorder (17 contrasts), (c) schizophrenia (39 contrasts) and, (d) healthy controls (46 contrasts); all of which satisfy current ALE power recommendations of including a minimum of 17 experiments (Eickhoff et al., 2017). We also performed contrast analyses and computed conjunctions among patient groups for the purpose of comparing across groups. Tables 1-3 include demographic details for each study and experiments corresponding to each *meta*-analysis.

For bipolar disorder, a total of 12 articles, 24 contrasts from 16 groups of 431 participants (currently in either euthymic, depressed or manic state) were deemed eligible. Nine articles considered eligible for major depressive disorder included 17 contrasts from 10 subject groups of 223 patients, 16 participants of which included psychotic symptoms (Garrett et al., 2011). The schizophrenia group comprised of 16 articles; 39 contrasts from 19 patient groups of 409 participants (including 56 schizophrenic patients with obsessive–compulsive disorder; Bleich-Cohen et al., 2014; Schirmbeck et al., 2014). A *meta*-analysis was also performed on healthy control participants by extracting coordinates from the within-subjects' contrasts of healthy participants reported from all eligible studies. In total, the healthy control group comprised 25 articles, 26 subject groups of 634 participants and 46 contrasts. Mean ages (±standard deviation) and gender proportions for each group were 36.98 ± 9.95 years and 50.8% male for patients with bipolar disorder, 39.17 ± 5.03 years and 48.8% male for patients with major depressive disorder, 32.93 ± 6.85 years and 74% male for schizophrenia patients and 34.49 ± 6.95 and 51.2% for the healthy control group. The age means and ranges for each original article are reported in Tables 1-3. The clinical details such as illness duration, illness severity and medication history related to the clinical samples included in the *meta*-analysis are reported in Supplemental Table 1.

## 3. Results

### 3.1. ALE maps

Table 4 shows a complete list of concordant activity for four independent *meta*-analyses on bipolar disorder, major depressive disorder, schizophrenia and healthy controls, as well as conjunction and contrast analyses for the corresponding groups. Data from each cluster are listed in order of cluster size MNI space identified by all ALE *meta*-analyses. Higher ALE values are indicative of a greater likelihood of activation. Significant results for separate patient groups compared to healthy controls are illustrated in Figs. 2-4, respectively.

**Table 1**
Information on source datasets included in the *meta*-analysis for bipolar disorder.

| Article | n | Male | Age Range | Mean (SD) | Foci | Task type | Contrast type |
|---|---|---|---|---|---|---|---|
| Alonso-Lana *et al.*, 2016 [ab] | 33 | 18 | NA | 44.13 (6.63) | 7 | Letter | 1 back > rest |
| | | | | | 1 | Letter | 2 back > rest |
| | | | | | 1 | Letter | 2 back > 1 back |
| Alonso-Lana *et al.*, 2016 [ab] | 28 | 17 | NA | 46.17 (7.4) | 3 | Letter | 1 back > rest |
| | | | | | 1 | Letter | 2 back > rest |
| | | | | | 3 | Letter | 2 back > 1 back |
| Dell'Osso *et al.*, 2015 | 28 | 15 | NA | 35.7 (9.2) | 7 | Letter | Linear trend |
| Drapier et al., 2008 [a] | 20 | 9 | 27–62 | 42.7 (10.4) | 5 | Letter | 1 back > rest |
| | | | | | 6 | Letter | 2 back > rest |
| | | | | | 4 | Letter | 3 back > rest |
| Fernandez *et al.*, 2013 | 41 | 23 | NA | 40.39 (10.2) | 5 | Letter | 2 back > rest |
| Frangou et al., 2008 | 7 | NA | NA | 37 (5.88) | 15 | Letter | Linear trend |
| Jogia et al., 2012 | 36 | 17 | 21–61 | 42.5 (10.6) | 14 | Letter | Linear trend |
| Miskowiak *et al.*, 2016 [a] | 56 | 35 | 18–65 | 39.5 (NA) | 6 | Visuospatial | 2 back > 0 back |
| | | | | | 4 | Visuospatial | 2 back > 1 back |
| Miskowiak *et al.*, 2017 | 64 | 26 | 18–65 | 37.6 (NA) | 13 | Visuospatial | 2 back > 1 back |
| Pavuluri *et al.*, 2012[b] | 10 | 5 | 12–18 | 12.4 (1.6) | 3 | Faces | 2 back > 0 back |
| Pavuluri *et al.*, 2012[b] | 11 | 7 | 12–18 | 13.1 (2.6) | 3 | Faces | 2 back > 0 back |
| Pomarol *et al.*, 2012 | 29 | 18 | 20–62 | 40.79 (12.08) | 7 | Letter | 2 back > rest |
| Rodriguez *et al.*, 2017 [a] | 26 | 10 | NA | 45.58 (9.23) | 3 | Shapes | 1 back > rest |
| | | | | | 2 | Shapes | 2 back > rest |
| Townsend et al., 2010[b] | 13 | 5 | NA | 38.5 (9.1) | 15 | Letter | 2 back > 0 back |
| Townsend et al., 2010[b] | 15 | 7 | NA | 37 (10.1) | 4 | Letter | 2 back > 0 back |
| Townsend et al., 2010[b] | 14 | 7 | NA | 38.7 (9.7) | 20 | Letter | 2 back > 0 back |

Note: n = sample size; SD = Standard deviation; NA = not available; [a] = article includes more than one contrast; [b] = article includes at least two groups

**Table 2**
Information on source datasets included in the *meta*-analysis for depression.

| Article | n | Male | Age range | Mean (SD) | Foci | Task type | Contrast type |
|---|---|---|---|---|---|---|---|
| Fitzgerald *et al.*, 2013 | 13 | 8 | NA | 38.4 | 7 | Letter | 2 back > 0 back |
| Garrett *et al.*, 2011 [ab] | 16 | 9 | NA | 34.13 | 12 | Letter | 1 back > 0 back |
| | | | | | 14 | Letter | 2 back > 0 back |
| Garrett *et al.*, 2011 [ab] | 15 | 5 | NA | 39.81 | 21 | Letter | 1 back > 0 back |
| | | | | | 5 | Letter | 2 back > 0 back |
| Harvey *et al.*, 2006 | 10 | 3 | NA | 33.8 | 8 | Letter | 3,2,1 back > 0 back |
| Miskowiak *et al.*, 2016 [a] | 56 | 35 | 18–65 | 39.5 | 6 | Visuospatial | 2 back > 0 back |
| | | | | | 4 | Visuospatial | 2 back > 1 back |
| Norbury *et al.*, 2014 | 15 | 7 | 21–61 | 39.5 | 5 | Letter | 3,2,1 back > 0 back |
| Rodriguez *et al.*, 2014 | 32 | 12 | NA | 46.5 | 9 | Letter | 2 back > rest |
| Rodriguez *et al.*, 2016 [a] | 26 | 10 | NA | 48.68 | 4 | Shapes | 1 back > rest |
| | | | | | 3 | Shapes | 2 back > rest |
| Schoning *et al.*, 2009 [a] | 28 | 12 | NA | 34.18 | 13 | Letter | 2 back > 0 back |
| | | | | | 28 | Letter | 2 back > 1 back |
| Walter et al., 2007 [a] | 12 | 8 | NA | 37.2 | 8 | Letter | 1 back > 0 back |
| | | | | | 9 | Letter | 2 back > 0 back |
| | | | | | 11 | Letter | 3 back > 0 back |

Note: n = sample size; R = Right handed; SD = Standard deviation; NA = not available; [a] = article includes more than one contrast comparing across task modality; [b] = article includes at least two groups

#### 3.1.1. Healthy controls

As a basis for the executive network of working memory, we first report the concordant brain activity from datasets of healthy controls extracted from all original articles. These regions include clusters within the bilateral parietal cortices and adjacent precuneus (Brodmann area [BA 7/40]), bilateral frontal cortices (BA 9), medial frontal cortex (BA 6), bilateral anterior insula (BA 13), left cerebellum, and left putamen. The largest cluster was the right parietal gyrus and the region that was most likely to be active was the right medial (labelled as superior) frontal gyrus (BA 8).

#### 3.1.2. Bipolar disorder

The *meta*-analysis representing bipolar disorder revealed the smallest number of clusters including bilateral parietal cortices (BA 40), left inferior frontal cortex (BA 9), and left cerebellum (see Fig. 2). A cluster within the left inferior parietal cortex was largest and most likely to be active. Note that no frontal activity was reported in the right frontal hemisphere.

#### 3.1.3. Major depressive disorder

Clusters reported in the *meta*-analysis from major depressive disorder patients included seven clusters; three of these clusters were found within the left and right middle (BA 6/46) and medial frontal cortices (BA 6; labelled as superior frontal gyrus in Table 4, see Fig. 3). The largest and most likely region to be active was the bilateral parietal cortices (BA 40). Other relevant clusters include the left and right cerebellum.

#### 3.1.4. Schizophrenia disorder

The *meta*-analysis of schizophrenia patients resulted in 11 clusters, yielding the largest number of clusters. Several clusters within the frontal lobe were highly likely to be active. The cluster that had the highest likelihood of activation was the right middle frontal cortex (BA 6). Other frontal clusters included the medial (labelled as superior)

**Table 3**
Information on source datasets included in the *meta*-analysis for schizophrenia.

| Article | n | Male | Age range | Mean (SD) | Foci | Task | Contrast type |
|---|---|---|---|---|---|---|---|
| Bleich-Cohen *et al.*, 2014 | 16 | 10 | 19–32 | 27 | 5 | Digit | 2 back > 0 back |
| Elsabagh *et al.*, 2009 [ab] | 15 | 15 | 18–60 | 41 (9.97) | 1 | Visuospatial | 0 back > rest |
| | | | | | 1 | Visuospatial | 2 back > 0 back |
| Elsabagh *et al.*, 2009 [ab] | 10 | 0 | 18–60 | 44.8 (9.68) | 1 | Visuospatial | 0 back > rest |
| | | | | | 1 | Visuospatial | 1 back > 0 back |
| | | | | | 3 | Visuospatial | 2 back > 0 back |
| Honey et al., 2002 | 20 | 20 | NA | 22.7 (5.91) | 7 | Letter | 2 back > 0 back |
| Jiang *et al.*, 2015 | 20 | 13 | NA | 22.7 (3.8) | 10 | Digit | 2 back > 0 back |
| Kumari *et al.*, 2006a [a] | 11 | 9 | NA | 42.55 (8.81) | 5 | Visuospatial | 0 back > rest |
| | | | | | 9 | Visuospatial | 1 back > rest |
| | | | | | 12 | Visuospatial | 2 back > rest |
| | | | | | 5 | Visuospatial | 1 back > 0 back |
| | | | | | 11 | Visuospatial | 2 back > 0 back |
| Kumari *et al.*, 2006b [ab] | 12 | 12 | 18–65 | 34 (4.86) | 11 | Visuospatial | 0 back > rest |
| | | | | | 10 | Visuospatial | 2 back > 0 back |
| Kumari *et al.*, 2006b [ab] | 13 | 13 | 18–65 | 33.85 (7.57) | 10 | Visuospatial | 0 back > rest |
| | | | | | 6 | Visuospatial | 1 back > 0 back |
| | | | | | 16 | Visuospatial | 2 back > 0 back |
| Kumari *et al.*, 2009 [a] | 36 | 29 | NA | 37.72 | 7 | Visuospatial | 0 back > rest |
| | | | | | 10 | Visuospatial | 1 back > rest |
| | | | | | 16 | Visuospatial | 2 back > rest |
| | | | | | 12 | Visuospatial | 1 back > 0 back |
| | | | | | 12 | Visuospatial | 2 back > 0 back |
| Mendrak *et al.*, 2004 | 12 | 9 | NA | 28.75 (9.13) | 13 | Letter | 2 back > 0 back |
| Orlov *et al.*, 2017 | 49 | 44 | NA | 35.35 | 20 | Letter | 3 back > 0 back |
| Royer *et al.*, 2009 | 19 | NA | 22–47 | 33 (6.9) | 21 | Digit | 2 back > 0 back |
| Sapara *et al.*, 2014 [ab] | 18 | 14 | 19–52 | 35.3 (9.92) | 15 | Visuospatial | 0 back > rest |
| | | | | | 7 | Visuospatial | 1 back > rest |
| | | | | | 13 | Visuospatial | 2 back > rest |
| | | | | | 7 | Visuospatial | 1 back > 0 back |
| | | | | | 9 | Visuospatial | 2 back > 0 back |
| Sapara *et al.*, 2014 [ab] | 14 | 9 | 26–49 | 37.7 | 5 | Visuospatial | 0 back > rest |
| | | | | | 12 | Visuospatial | 1 back > rest |
| | | | | | 10 | Visuospatial | 2 back > rest |
| Schirmbeck *et al.*, 2014 | 40 | 30 | NA | 39.5 | 23 | Digit | 2 back > 0 back |
| Vogel *et al.*, 2016[b] | 22 | 22 | NA | 28.4 (7.3) | 1 | Letter | 2 back > 0 back |
| Vogel *et al.*, 2016[b] | 20 | 20 | NA | 33.5 (7.2) | 8 | Letter | 2 back > 0 back |
| Wu *et al.*, 2017 | 45 | 24 | NA | 24.16 (5.2) | 5 | Digit | 2 back > 0 back |
| Zhou *et al.*, 2014 | 17 | 10 | 18–45 | 23.71 (6.89) | 9 | Letter | 2 back > 0 back |

Note: n = sample size; SD = Standard deviation; NA = not available; [a] = article includes more than one contrast; [b] = article includes at least two groups.

frontal gyrus (BA 8), two clusters within the right middle cortices (BA 9/46), and two clusters within the left middle frontal gyrus (BA 6/9), see Fig. 4. The largest two clusters were within the left and right parietal cortex (BA 40). An additional cluster was found within the left superior parietal cortex (BA 7). Finally, the *meta*-analysis for the schizophrenia group also yielded concordant activity in left and right cerebellum.

#### 3.1.5. Conjunction analysis

Conjunction analysis was performed between groups. Regions that were shown in all groups, as evident by the conjunction analyses include the bilateral parietal clusters (BA 40), left middle frontal cortex (BA 9/46), and left cerebellum. Regions that overlapped between groups excluding bipolar disorder included the right middle frontal cortex (BA 6) and medial (superior) frontal cortex (BA 6/8). In addition, the left middle frontal cortex (BA 6) and right superior frontal cortex (BA 9) were found in both schizophrenia patients and healthy control participants.

#### 3.1.6. Contrast analysis

The contrast analysis was performed to reveal activation with respect to each clinical group, i.e., exceeded/reduced concordant activation between patient and healthy participants. Comparing between bipolar disorder and healthy controls, no suprathreshold activity was found for bipolar disorder, suggesting no hyperactivity for the bipolar disorder group. The reverse contrast yielded greater concordant activation within the medial frontal cortex (BA 6/8), and bilateral middle frontal cortex (BA 6/8). Comparing depression with healthy controls, greater activation within the right inferior parietal cortex (BA 40) and right superior/ middle frontal gyrus (BA 6/10) was found, indicating hyperactivity. The reverse contrast revealed no significant clusters. The comparison between schizophrenia and healthy controls revealed the largest count of clusters such as several clusters within the bilateral inferior parietal cortex and precuneus (BA 7/40), left middle frontal clusters (BA 6/9/46) and the right cerebellum. No clusters above thresholding were statistically significant for the control > schizophrenia contrast. Comparisons between groups are reported in Table 4.

### 3.2. Controlling for working memory load

Since the variation of studies reporting hypo- and hyperactivation of the frontal lobe in schizophrenia patients may be attributed to differences in working memory load (Callicott et al., 2000, 2003; Barch, 2005), we aimed to repeat the *meta*-analyses for schizophrenia and healthy controls extracting foci from 2 > 0 back only. Supplemental Table 2 lists the reported results from schizophrenia and healthy controls along with the contrast and conjunction analysis.

#### 3.2.1. Healthy controls (2 > 0 back only)

The *meta*-analysis on healthy controls 2 > 0 back revealed activity within the bilateral middle frontal cortex (BA 6/9), medial prefrontal cortex (BA 6/8), left parietal cortex (BA 40), right insula (BA 47), left putamen and left middle frontal cortex (BA 6). Differences compared to the main *meta*-analysis were the absence of right parietal cortex (BA 7/

**Table 4**
Concordant brain regions related to working memory.

| **Meta-analyses** | | | | | | |
|---|---|---|---|---|---|---|
| *Healthy controls* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| 1 | 4008 | 0.034 | 46 | −46 | 44 | R Inferior Parietal Gyrus BA 40 |
| 2 | 3848 | 0.035 | −40 | −44 | 42 | L Inferior Parietal Gyrus BA 40 |
| 3 | 3456 | 0.024 | −48 | 10 | 28 | L Inferior Frontal Gyrus BA 9 |
| 4 | 3440 | 0.043 | 2 | 18 | 48 | R Superior Frontal Gyrus BA 8 |
| 5 | 3160 | 0.034 | 30 | 8 | 56 | R Middle Frontal Gyrus BA 6 |
| 6 | 1752 | 0.023 | 42 | 34 | 28 | R Superior Frontal Gyrus BA 9 |
| 7 | 1664 | 0.033 | 36 | 22 | 0 | R Insula BA 13 |
| 8 | 1528 | 0.031 | −18 | 0 | 10 | L Putamen |
| 9 | 1216 | 0.031 | −30 | 24 | 0 | L Insula BA 13 |
| 10 | 1064 | 0.021 | −34 | −60 | −34 | L Cerebellum (Tonsil) |
| 11 | 1008 | 0.026 | 12 | −62 | 52 | R Precuneus BA 7 |
| *Bipolar* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| 1 | 3648 | 0.029 | −42 | −44 | 42 | L Inferior Parietal Gyrus BA 40 |
| 2 | 1760 | 0.022 | 34 | −52 | 42 | R Inferior Parietal Gyrus BA 40 |
| 3 | 1096 | 0.018 | −44 | 4 | 28 | L Inferior Frontal Gyrus BA 9 |
| 4 | 936 | 0.021 | −38 | −60 | −26 | L Cerebellum (Tuber) |
| *Depression* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| 1 | 3800 | 0.024 | 42 | −48 | 46 | R Inferior Parietal Gyrus BA 40 |
| 2 | 2440 | 0.019 | −36 | −50 | 46 | L Inferior Parietal Gyrus BA 40 |
| 3 | 704 | 0.016 | 30 | −66 | –32 | R Cerebellum (Tonsil) |
| 4 | 696 | 0.014 | 26 | 2 | 50 | R Middle Frontal Gyrus BA 6 |
| 5 | 688 | 0.014 | –32 | −68 | −34 | L Cerebellum (Pyramis) |
| 6 | 648 | 0.018 | 2 | 8 | 56 | R Superior Frontal Gyrus BA 6 |
| 7 | 640 | 0.014 | −46 | 26 | 22 | L Middle Frontal Gyrus BA 46 |
| *Schizophrenia* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| 1 | 6296 | 0.030 | 48 | −42 | 46 | R Inferior Parietal Gyrus BA 40 |
| 2 | 6200 | 0.029 | −44 | −44 | 50 | L Inferior Parietal Gyrus BA 40 |
| 3 | 3528 | 0.033 | 30 | 6 | 54 | R Middle Frontal Gyrus BA 6 |
| 4 | 2248 | 0.019 | −44 | 2 | 48 | L Middle Frontal Gyrus BA 6 |
| 5 | 2000 | 0.031 | 4 | 20 | 48 | R Superior Frontal Gyrus BA 8 |
| 6 | 1864 | 0.034 | 44 | 38 | 26 | R Middle Frontal Gyrus BA 46 |
| 7 | 1752 | 0.027 | 32 | −58 | −28 | R Cerebellum (Tuber) |
| 8 | 1288 | 0.020 | 50 | 14 | 32 | R Middle Frontal Gyrus BA 9 |
| 9 | 1080 | 0.019 | −12 | −64 | 56 | L Superior Parietal Gyrus BA 7 |
| 10 | 1072 | 0.026 | −46 | 28 | 28 | L Middle Frontal Gyrus BA 9 |
| 11 | 1056 | 0.027 | −30 | −60 | −34 | L Cerebellum (Tonsil) |
| **Conjunctions** | | | | | | |
| *Bipolar-AND-Healthy Controls* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| 1 | 2072 | 0.029 | −42 | −44 | 42 | L Inferior Parietal Gyrus BA 40 |
| 2 | 408 | 0.017 | −42 | 14 | 28 | L Middle Frontal Gyrus BA 9 |
| 3 | 400 | 0.018 | 36 | −52 | 44 | R Inferior Parietal Gyrus BA 40 |
| 4 | 104 | 0.014 | −34 | −62 | −28 | L Cerebellum (Tuber) |
| *Depression-AND-Healthy Controls* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| 1 | 2080 | 0.023 | 46 | −46 | 46 | R Inferior Parietal Gyrus BA 40 |
| 2 | 1696 | 0.019 | −36 | −50 | 46 | L Inferior Parietal Gyrus BA 40 |
| 3 | 432 | 0.017 | 0 | 8 | 56 | L Superior Frontal Gyrus BA 6 |
| 4 | 352 | 0.013 | −46 | 24 | 22 | L Middle Frontal Gyrus BA 46 |
| 5 | 240 | 0.013 | 32 | 2 | 50 | R Middle Frontal Gyrus BA 6 |
| 6 | 160 | 0.014 | −34 | −64 | −30 | L Cerebellum (Tuber) |
| *Schizophrenia-AND-Healthy Controls* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| 1 | 2176 | 0.026 | 46 | −42 | 46 | R Inferior Parietal Gyrus BA 40 |
| 2 | 1720 | 0.033 | 30 | 6 | 56 | R Middle Frontal Gyrus BA 6 |
| 3 | 1640 | 0.022 | −44 | −44 | 46 | L Inferior Parietal Gyrus BA 40 |
| 4 | 1480 | 0.031 | 4 | 20 | 48 | R Superior Frontal Gyrus BA 8 |
| 5 | 968 | 0.023 | 42 | 36 | 28 | R Superior Frontal Gyrus BA 9 |
| 6 | 736 | 0.020 | –32 | −60 | −34 | L Cerebellum (Tonsil) |
| 7 | 448 | 0.019 | −44 | 2 | 48 | L Middle Frontal Gyrus BA 6 |
| 8 | 80 | 0.015 | −44 | 26 | 24 | L Middle Frontal Gyrus BA 46 |
| *Bipolar-and-depression* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| 1 | 1520 | 0.019 | −36 | −50 | 46 | L Inferior Parietal Gyrus BA 40 |
| 2 | 928 | 0.016 | 34 | −58 | 36 | R Angular Gyrus BA 39 |
| 3 | 192 | 0.014 | −36 | −64 | −28 | L Cerebellum (Tuber) |
| *Bipolar-AND-Schizophrenia* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| 1 | 1376 | 0.021 | −44 | −46 | 44 | L Inferior Parietal Gyrus BA 40 |

(*continued on next page*)

**Table 4** (*continued*)

| | | | | | | |
|---|---|---|---|---|---|---|
| **Meta-analyses** | | | | | | |
| *Healthy controls* | | | | | | |
| 2 | 240 | 0.014 | 36 | −50 | 50 | R Inferior Parietal Gyrus BA 40 |
| 3 | 72 | 0.014 | −36 | −62 | −30 | L Cerebellum (Tuber) |
| *Depression-AND-Schizophrenia* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| 1 | 1904 | 0.022 | 46 | −44 | 46 | R Inferior Parietal Gyrus BA 40 |
| 2 | 856 | 0.015 | −38 | −50 | 40 | L Inferior Parietal Gyrus BA 40 |
| 3 | 472 | 0.014 | 26 | 2 | 52 | R Middle Frontal Gyrus BA 6 |
| 4 | 208 | 0.014 | −46 | 26 | 22 | L Middle Frontal Gyrus BA 46 |
| 5 | 120 | 0.013 | −34 | −64 | –32 | L Cerebellum (Tonsil) |
| **Contrasts** | | | | | | |
| *Bipolar > Healthy Controls* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| no suprathreshold clusters | | | | | | |
| *Bipolar > Depression* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| no suprathreshold clusters | | | | | | |
| *Bipolar > Schizophrenia* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| no suprathreshold clusters | | | | | | |
| *Healthy Controls > Bipolar* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| 1 | 1560 | 3.090 | −4 | 16 | 50 | L Superior Frontal Gyrus BA 8 |
| 2 | 1016 | 3.121 | 36 | 6 | 52 | R Middle Frontal Gyrus BA 6 |
| 3 | 952 | 3.719 | −44 | −1 | 51 | L Middle Frontal Gyrus BA 6 |
| *Healthy Controls > Depression* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| no suprathreshold clusters | | | | | | |
| *Healthy Controls > Schizophrenia* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| no suprathreshold clusters | | | | | | |
| *Depression > Bipolar* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| 1 | 112 | 2.575 | 42 | −48 | 45 | R Inferior Parietal Gyrus BA 40 |
| 2 | 80 | 2.619 | 32 | 8 | 48 | R Middle Frontal Gyrus BA 6 |
| *Depression > Healthy Controls* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| 1 | 256 | 2.820 | 36 | −54 | 34 | R Inferior Parietal Gyrus BA 40 |
| 2 | 120 | 2.878 | 40 | 50 | 20 | R Superior Frontal Gyrus BA 10 |
| 3 | 56 | 2.597 | 28 | 2 | 48 | R Middle Frontal Gyrus BA 6 |
| *Depression > Schizophrenia* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| no suprathreshold clusters | | | | | | |
| *Schizophrenia > Bipolar* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| 1 | 2608 | 3.890 | −44 | −26 | 52 | L Inferior Parietal Gyrus BA 40 |
| 2 | 2032 | 3.431 | −38 | −7 | 53 | R Middle Frontal Gyrus BA 6 |
| 3 | 1856 | 3.090 | 31 | 9 | 52 | R Middle Frontal Gyrus BA 6 |
| 4 | 1400 | 3.035 | 1 | 15 | 47 | R Medial Frontal Gyrus BA 6 |
| 5 | 808 | 2.911 | 24 | −67 | 50 | R Precuneus BA 7 |
| 6 | 688 | 3.238 | 24 | −51 | −28 | R Cerebellum (Anterior) |
| 7 | 520 | 3.238 | 44 | −34 | 44 | R Inferior Parietal Gyrus BA 40 |
| 8 | 152 | 2.678 | −14 | −66 | 50 | L Precuneus BA 7 |
| 9 | 80 | 2.652 | 42 | 38 | 34 | R Middle Frontal Gyrus BA 9 |
| *Schizophrenia > Healthy Controls* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| 1 | 536 | 3.290 | −46 | −34 | 56 | L Inferior Parietal Gyrus BA 40 |
| 2 | 320 | 3.090 | 50 | −38 | 42 | R Inferior Parietal Gyrus BA 40 |
| 3 | 312 | 2.604 | −31 | −6 | 60 | L Middle Frontal Gyrus BA 6 |
| 4 | 168 | 2.929 | −50 | 24 | 34 | L Middle Frontal Gyrus BA 9 |
| 5 | 128 | 2.862 | −48 | −52 | 46 | L Inferior Parietal Gyrus BA 40 |
| 6 | 96 | 2.568 | 36 | −56 | −26 | R Cerebellum (Culmen) |
| 7 | 88 | 2.678 | 28 | −56 | 50 | R Precuneus BA 7 |
| 8 | 80 | 2.706 | 22 | −66 | 50 | R Precuneus BA 7 |
| 9 | 80 | 2.489 | 26 | −4 | 54 | R Sub-Gyral Matter BA 7 |
| *Schizophrenia > Depression* | | | | | | |
| Cluster # | Volume $mm^3$ | ALE Value | x | y | z | Brain region |
| 1 | 200 | 2.478 | 28 | −52 | −26 | R Cerebellum (Culmen) |
| 2 | 8 | 2.382 | −48 | −38 | 56 | L Inferior Parietal Gyrus BA 40 |

Note: Talairach coordinates (x, y, z) of brain regions surviving a cluster-level threshold of $p < 0.05$ and a cluster forming threshold of $p < 0.01$ for single studies. Contrast threshold was set to $p = 0.01$, 5000 permutations, $> 50\ mm^3$, L = Left, R = Right; v = ventral; d = dorsal; BA = Brodmann Area, ALE = Activation Likelihood Estimate.

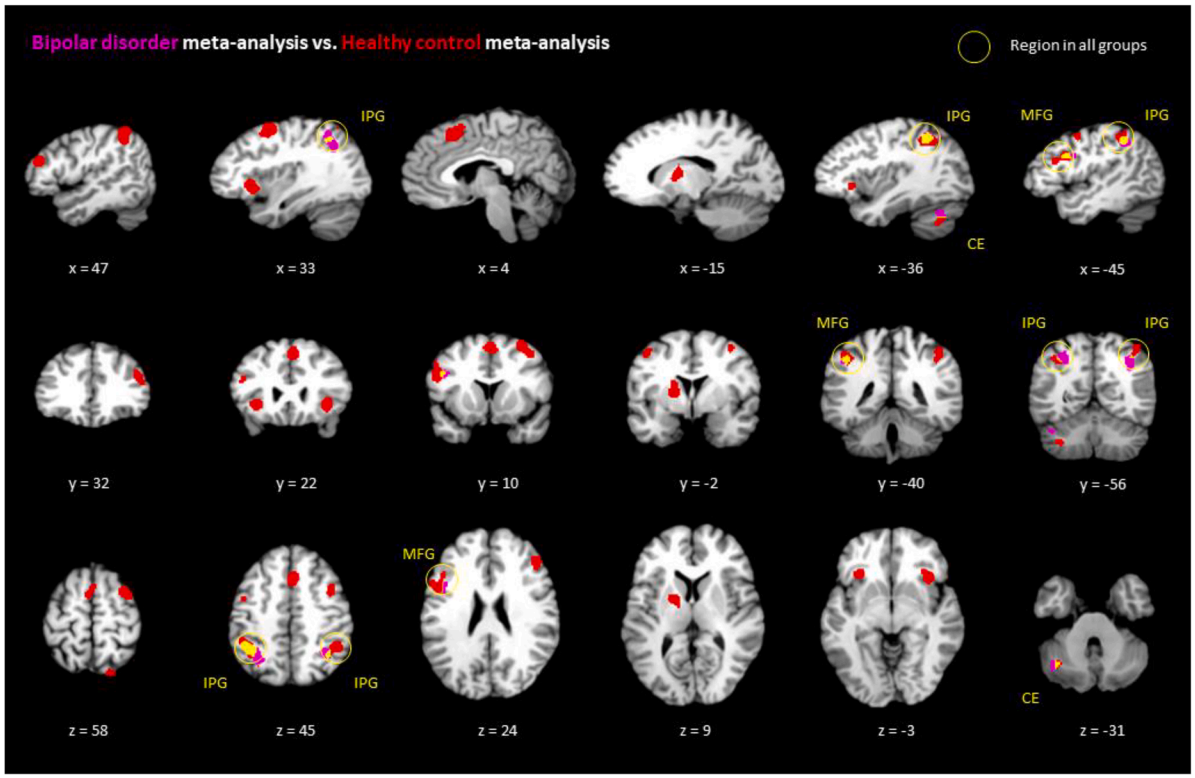


**Fig. 2.** Concordant brain activity of n-back across studies for bipolar disorder displayed as sagittal, coronal and axial slices. Clusters from the bipolar disorder group are displayed in magenta, healthy controls are displayed in red. Yellow circles reflect regions concordant in all groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

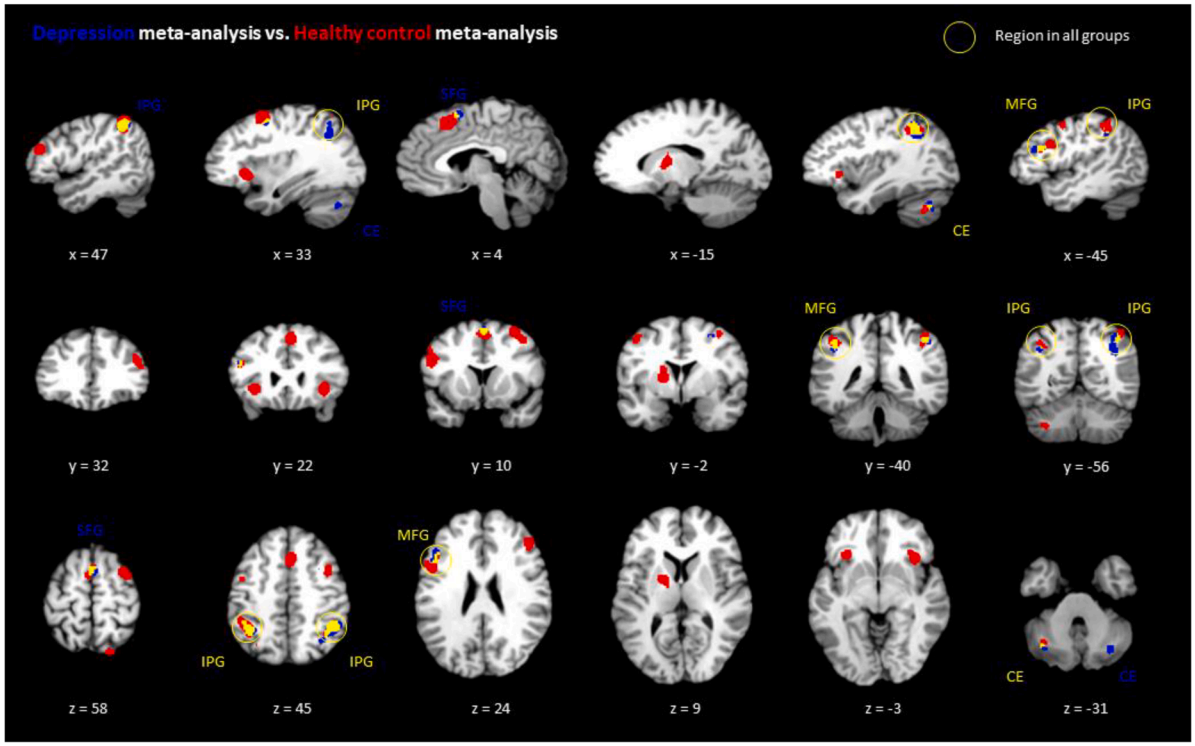


**Fig. 3.** Concordant brain activity of n-back across studies for depression disorder displayed as sagittal, coronal and axial slices. Clusters from the depression disorder group are displayed in blue, healthy controls are displayed in red. Yellow circles reflect regions concordant in all groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

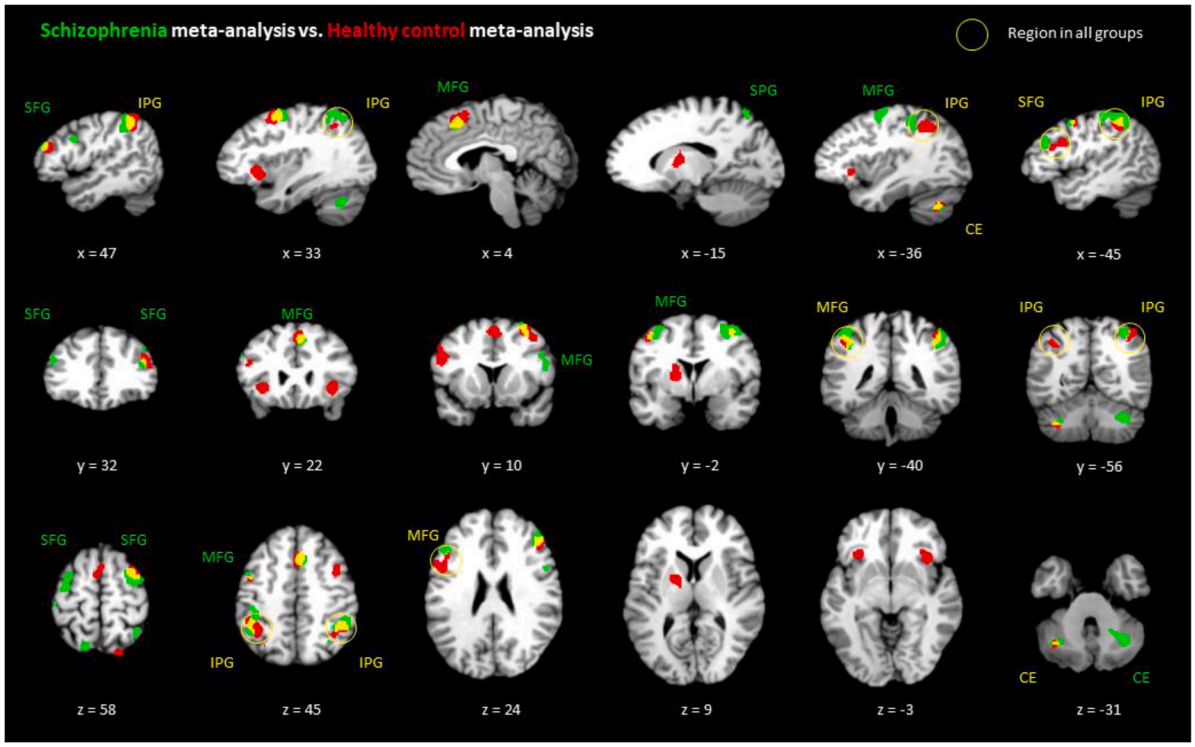


**Fig. 4.** Concordant brain activity of n-back across studies for schizophrenia displayed as sagittal, coronal and axial slices. Clusters from the schizophrenia group are displayed in green, healthy controls are displayed in red. Yellow circles reflect regions concordant in all groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

40), left anterior insula (BA 13), and left cerebellum. Supplemental Table 2 displays coordinates and voxel count for each cluster. Supplemental Table 2 displays the foci reported in the schizophrenia group with 2 > 0 back contrasts only.

### 3.2.2. *Schizophrenia (2 > 0 back only)*

The follow-up analysis of 2 > 0 back in the schizophrenia group revealed clusters within the parietal cortex (BA 7/40), medial prefrontal cortex (BA 8), the bilateral middle frontal cortex (BA 9/44/46), and right middle frontal gyrus (BA6). All but left middle frontal (BA 6) and bilateral cerebellar clusters yielded from the main analysis were present in the 2 > 0 analysis (see Supplemental Table 2 for details).

### 3.2.3. *Conjunction analysis (2 > 0 back only)*

When controlling for working memory load, both groups revealed concordant clusters within the medial frontal cortex (BA 8), bilateral middle frontal gyrus (BA 6/9), and left inferior parietal cortex (BA 40). These four clusters overlapped with the conjunction analysis produced when including all n-back contrasts, yet lacked activity within the right parietal cortex (BA 7/40), left cerebellum, and left middle frontal cortex (BA 6/46); thereby complimenting the differences between the main analysis and 2 > 0 back only analysis for each group (see Table 1 and Supplemental Table 2).

### 3.2.4. *Contrast analysis (2 > 0 back only)*

By comparing schizophrenia and healthy controls, schizophrenia appeared to yield greater activity within the right inferior parietal cortex (BA 40). However, for the healthy controls > schizophrenia contrast, this analysis resulted in no suprathreshold clusters. Supplemental Table 2 displays coordinates and voxel count for the contrast analyses.

## 4. Discussion

The present study used a transdiagnostic *meta*-analytic approach (ALE) to examine the neural representations of working memory across schizophrenia, bipolar disorder and major depressive disorder. To assess concordant activation for these clinical disorders, we limited our search to perform *meta*-analyses on within-subjects' contrasts (i.e., contrasts associated with the n-back task) for these disorders and we then compared with a *meta*-analysis on healthy participants extracted from all eligible articles. Interestingly, a rapid growing increase of original transdiagnostic studies (Huang et al., 2020; Li et al., 2019; Qi et al., 2020; Ma et al., 2020; Lerman-Sinkoff et al., 2019; Baker et al., 2019), *meta*-analyses (Sha et al., 2018; McTeague et al., 2020) and reviews (Dezhina et al., 2019; Birur et al., 2017) have revealed the shared abnormalities in brain structure, function and connectivity across multiple psychiatric disorders. Here our results revealed that bilateral insula and left striatum were blunted in all patient groups, suggesting the likelihood of decreased activity of these subcortical areas.

Empirical support for changes in striatum activation derive from studies investigating mood disorders (Ng et al., 2019) and schizophrenia (Brugger et al., 2020). Among these studies, inconsistencies of activation or deactivation of the striatum may depend on its dorsal and ventral counterparts. For example, while *reduced* right ventral striatum becomes active during reward anticipation (Esslinger et al., 2012), *enhanced* dorsal striatum activity became active when anticipating affective stimuli in a working memory task (Li et al., 2014).

The anterior insula is another anatomical deep region attributed to anticipation of likely events (Samanez-Larkin, et al., 2007; Liu et al., 2011) and is located beneath the frontal lobe and operculum. The anterior insula is an essential region anatomically positioned to serve multiple functions. Specifically, the anterior insula coactivates with and connects with the frontal, parietal, and temporal cortex as well as subcortical regions such as the thalamus, hippocampus, amygdala and putamen (Ghaziri et al., 2018). Prior *meta*-analyses have shown that recruitment of the insula is essential to facilitate working memory processes especially during developmental stages and older adulthood, perhaps serving as a substitute for frontal lobe inactivity (Rottschy et al.,

2012; Yaple and Arsalidou, 2018; Yaple et al., 2019).

Taken together, the striatum and anterior insula cortex may play a functional role in the anticipation of updating stimuli, supported by patients with affective symptoms displaying negative attitudes towards anticipated events (Beck, 1979; Abler et al., 2007), and whom display reduced or enhanced activity in the anterior insula (Strigo et al., 2013; Hammar et al., 2016), anterior cingulate cortex (Smoski et al., 2009; Dichter et al., 2012; Chase et al., 2013; Tolomeo et al., 2016; Kollmann et al., 2017), and striatum (Smoski et al., 2009; Olino et al., 2011; Nusslock et al., 2012; Schreiter et al., 2016) when anticipating upcoming events. Alternatively, we propose that blunted striatum and anterior insula might be considered the neural substrates responsible to capture the impaired working memory across schizophrenia, bipolar and major depressive disorders.

Interestingly, the current findings revealed that the inferior parietal gyrus (BA 40) is activated in the patient groups. Indeed, unilateral lesions in the inferior parietal cortex often result in hemispatial neglect and failure to direct attention towards locations in any regions of space (Corbetta et al., 2002). Throughout the following sections, we discuss these findings and highlight other key findings associated with each group.

### 4.1. Schizophrenia

Previous schizophrenia studies reported increased and decreased activity of the dorsolateral prefrontal cortex (Manoach et al., 1999, 2000; Callicott et al., 2000, 2003; Quintana et al., 2003; Sabri et al., 2003; Jansma et al., 2004; Holmes et al., 2005; Karlsgodt et al., 2007; Wolf et al., 2011; Poppe et al., 2016). Since prior *meta*-analyses show analogous findings, albeit with insufficient sample sizes (Glahn et al., 2005; Minzenberg et al., 2009), we hypothesized that schizophrenia patients performing the n-back task would yield decreased and increased activity of the frontal cortex. Inconsistencies of findings have reported either no activity in the frontal cortex in schizophrenia patients in comparison with controls (Honey et al., 2002; Walter et al., 2003; Kindermann et al., 2004), or a combination of both activation or deactivation (Callicott et al., 2000, 2003; Manoach et al., 2000; Quintana et al., 2003; Sabri et al., 2003; Jansma et al., 2004; see Barch, 2005 for review).

Some have suggested that differences among studies depend on the variation of working memory between studies (Callicott et al., 2000, 2003; Barch, 2005). We tested this hypothesis by performing an additional *meta*-analysis on $2 > 0$ back only and then comparing it with the main analysis by visual inspection (See Supplemental Table 1). The $2 > 0$ back *meta*-analysis revealed hyperactive clusters within the right inferior frontal cortex and right parietal cortex and one smaller hypoactive cluster within the left middle frontal lobe, which has been previously suggested as a candidate endophenotype for schizophrenia (Zhang et al., 2016). When controlling for working memory load, schizophrenia patients yield both increase activity of the right frontal-parietal network and to a smaller degree, decrease activity of the left frontal cortex supporting the hypothesis that schizophrenia patients yield both decreased and increased activity of the frontal cortex.

Notably, it was previously suggested that increased activity of the frontal lobe may be attributed to psychotic symptoms (Corlett et al., 2007). A recent study provided partial evidence for this claim by demonstrating increased activity within clinical high-risk patients with psychosis (Thermenos et al., 2016); however, it is also important to acknowledge that multiple factors can contribute to brain alterations including the type of and exposure to administered medication as well as the chronological stage of the disorder (Gong et al., 2015). For example, a person with a history of psychotic medication use may exhibit increased activity of the frontal lobewhile a naïve medicated first episode schizophrenic patient may have suspected neuronal overgrowth, a deficit in normal pruning during neurogenesis (Radua et al., 2012; see Gong et al., 2015 for review). A third possible neural mechanism maybe that one hemisphere may be compensating for the other in the attempt to maintain working memory performance (Tan et al., 2006; Karlsgodt et al., 2009; Wolf et al., 2011). However, without longitudinal studies, this hypothesis has yet to be explored across different clinical stages for both medicated and non-medicated patients under similar conditions of working memory load.

### 4.2. Major depressive disorder

Among the literature, patients with major depressive disorder have been found to exhibit both deactivations of the dorsolateral prefrontal cortex and activation of ventrolateral prefrontal cortex (Brody et al., 2001; Rogers et al., 2004). Moreover, one study reported changes in activation direction depending on the context of emotional stimuli (Dichter et al., 2009). We know from prior empirical studies that major depressive disorder patients typically display negative attitudes towards anticipated events (Beck, 1979; Abler et al., 2007), which would explain the lack of left putamen and bilateral insula as similar to the bipolar and schizophrenia groups. However, the major depressive disorder group deviates from the other groups with regards to hyperactivity of two clusters within the frontal and parietal lobes when contrasting major depressive disorder and healthy controls.

It has been suggested that the frontal-parietal network is recruited to update upcoming endogenous stimuli representations (Sohn et al., 2005; Cole and Schneider, 2007; Borst and Anderson, 2012; Fair et al., 2009) and maintains relevant contextual information in mind (Rowe and Passingham, 2001; Veltman et al., 2003; Woodward et al., 2006; Smith et al., 2017; Fair et al., 2009). However, some declare that the fronto-parietal executive network specifically operates as a rapid adaptive control system (Dosenbach et al., 2007, 2008; Velanova et al., 2008; Fair et al., 2009; Gratton et al., 2017), which can be distinguished into a left and right frontoparietal network operating during the pre-and post-decision-making period, respectively (Gratton et al., 2017). The current *meta*-analysis revealed activity of the right frontal and parietal clusters, which may indicate that patients with major depressive disorder have dysfunctional adaptive control system operations occurring after a response has been made. It is during this post-decision period in which response evaluation, feedback implementation, or trial adjustments occur (Gratton et al., 2017). This may suggest that the right-lateralized frontal and parietal clusters found in the *meta*-analysis in major depressive disorder patients may be linked to the 'catastrophic response to failure' (Beats et al., 1996), defined as a lack of willingness to adapt to more sustainable strategies after receiving negative feedback (Elliott et al., 1996, 1997; Taylor Tavares et al., 2008; Douglas et al., 2009). However, due to the limitation of the *meta*-analysis approach, we find that this hypothesis deserves further empirical attention to examine the neural mechanisms associated with an adaptive control system in major depressive disorder patients.

### 4.3. Bipolar disorder

Inconsistent reports of frontal lobe activation in bipolar disorder patients and healthy controls include decreases and increases of the frontal cortex (e.g., Adler et al., 2004; Drapier et al., 2008; Thermenos et al., 2010; Jogia et al., 2011), increase activity of the right medial frontal gyri (Monks et al., 2004), hypoactivation the left frontal lobe (Monks et al., 2004), and decrease activity of the left and right dorsolateral prefrontal cortex (Frangou et al., 2008; Hamilton et al., 2009; Townsend et al., 2010). Therefore, prior literature not only varies with the location of frontal activation but also hemispheric lateralization, as well as the direction of the contrast (i.e., $2 > 0$ back and $0 < 2$ back).

Despite the reported variation of frontal activity across studies when compiling between-group differences (Cremaschi et al., 2013), the current results revealed a left-lateralized frontal cluster in the bipolar disorder *meta*-analysis, specifically within the inferior gyrus. Note, however, that the left inferior gyrus was also active in all other patient

and healthy groups, suggesting this region may operate as a core region of the working memory executive network and may not be exceptional to bipolar disorder patients. All regions reported by the bipolar disorder *meta*-analysis were also reported in the healthy control group, while no activity was found in bipolar disorder greater than healthy controls. This implies that decreased activity (but not increased) in bipolar patients is more likely to be found in any given empirical experiment.

Important regions that were blunted in the bipolar disorder group included the medial frontal cortex and right inferior cortex; regions that are often associated with performance monitoring (Ullsperger, 2006; Crone, 2014; Ninomiya et al., 2018) and inhibition of irrelevant stimuli (Garavan et al. 2002; Aron and Poldrack, 2006; Chevrier et al., 2007; McNab et al., 2008; Zheng et al., 2008; Dambacher et al., 2014; see Hung et al., 2018 for *meta*-analysis), respectively. Perhaps these findings relate to the decrease in working memory abilities in patients suffering from bipolar disorder (Torrent et al., 2006; Dittmann et al., 2008; Hsiao et al., 2009; Solé et al., 2011, 2012; Pålsson et al., 2013). These patterns may be explained by changes in monitor and control mechanisms (Melcher et al., 2008; Morsel et al., 2014), or a reduced ability to inhibit irrelevant stimuli (e.g., Murphy et al., 1999; Haldane et al., 2008; Robinson et al., 2013; Roberts et al., 2013; Vierck, 2015; Bora et al., 2016; Lozano et al., 2016).

Intact areas include those within the 'frontal-parietal' network, i.e., core areas associated with working memory processing (Owen et al., 2005; Rottschy et al., 2012; Yaple and Arsalidou, 2018). This network appeared to be left-lateralized and focalized to the left inferior frontal cortex (BA 9) and bilateral inferior parietal cortex. Interestingly, these areas have been shown to operate together to facilitate updating (Sohn et al., 2005; Cole and Schneider, 2007; Borst and Anderson, 2012; Fair et al., 2009) and maintenance of relevant contextual information (Rowe and Passingham, 2001; Veltman et al., 2003; Woodward et al., 2006; Smith et al., 2017; Fair et al., 2009). Some have declared that executive networks such as the frontoparietal and cingulo-opercular networks may account for multiple executive operations or may operate together during a single cognitive process (Dosenbach et al., 2007, 2008; Velanova et al., 2008; Fair et al., 2009; Gratton et al., 2017). Specifically, the frontal-parietal network facilitates rapid adaptive control, while the cingulo-opercular network is recruited during long-term stable set maintenance (Fair et al., 2009). Since concordant frontal and parietal areas appear to be intact while regions within the cingulo-opercular network were absent in the bipolar disorder group, we speculate that adaptive control mechanisms may also be sustained, while maintenance mechanisms may be dysfunctional; however, to our knowledge, this has yet to be explored in an empirical setting.

### 4.4. Limitations

Working memory performance via the n-back task involves a wide number of functions such as updating, manipulation, maintenance, and inhibition (Yaple et al., 2019). For instance, the "0-back minus rest" contrast would be expected to draw mainly upon identification and maintenance processes because the criterion stimulus (e.g., the letter X) must be maintained in working memory for the duration of the task. A 1-back contrast would draw upon additional updating processes since every stimulus serves as the criterion for the subsequent trial requiring further updating. A 2-back contrast would draw upon identification, maintenance, updating, as well as inhibition of distractors between the initial item and the 2-back item. Therefore, the results of the *meta*-analyses may reflect co-activation of multiple processes and hence distinct executive networks. Notably, we attempted to reduce study heterogeneity by including only fMRI experiments that used the n-back task. Due to the required sufficient number of contrasts compiled from each clinical group, we performed *meta*-analyses specifically focusing on schizophrenia, bipolar disorder and major depressive disorder.

### 4.5. Conclusions

The current *meta*-analysis identified several alterations in clinical populations that exhibit both psychotic and mood disorder symptoms, specifically we found blunted insula, putamen and frontal lobe.

Based on empirical studies we suggest that specific working memory processes may be hindered by specific impaired neural mechanisms. These neural mechanisms may include the ability to anticipate the updating of novel stimuli (Yu et al., 2013) associated with subcortical regions such as the putamen and insulae maintenance and updating of stimuli controlled by certain executive networks (i.e. the frontal-parietal and cingulo-opercular network, respectively; Dosenbach et al., 2007, 2008; Velanova et al., 2008; Fair et al., 2009; Gratton et al., 2017), and inhibition of irrelevant stimuli attributed to the right inferior frontal region (Aron and Poldrack, 2006; Chevrier et al., 2007; McNab et al., 2008; Zheng et al., 2008; Dambacher et al., 2014; Hung et al., 2018). Given that certain disorders across studies reveal hypo- and hyper-activation among specific networks, these processes may affect partially or fully, depending on the specific role of each region afflicted and whether other regions are able to compensate for neural dysfunction (Tan et al., 2006; Karlsgodt et al., 2009; Wolf et al., 2011). Due to the indirect nature of the *meta*-analytic approach, our conclusions are not definitive and thus we encourage more empirical work to shed light on these specific working memory mechanisms. Nevertheless, our goal is to establish the likelihood of whether the same brain networks were compromised in schizophrenia and mood disorders. However, more research is needed before the neurobiological substrates can be implemented in future revisions of the Diagnostic and Statistical Manual of Mental Disorder and to better optimise pharmacological treatment outcomes.

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## CRediT authorship contribution statement

**Zachary Adam Yaple:** . **Serenella Tolomeo:** Conceptualization, Methodology, Investigation, Writing – original draft;. **Rongjun Yu:** Resources, Supervision, Writing – review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102747.

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