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# Neural Correlates of N-back Task Performance and Proposal for Corresponding Neuromodulation Targets in Psychiatric and Neurodevelopmental Disorders

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## Abstract

**AIM:** Working Memory (WM) deficit represents the most common cognitive impairment in psychiatric and neurodevelopmental disorders, making the identification of its neural substrates a crucial step towards the conceptualization of restorative interventions. Here we present a meta-analysis focusing on neural activations associated with the most commonly used task to measure WM, the N-back task, in patients with Schizophrenia, Depressive Disorder, Bipolar Disorder, and Attention Deficit Hyperactivity Disorder (ADHD). Showing qualitative similarities and differences in WM processing between patients and healthy controls, we propose possible targets for cognitive enhancement approaches.

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AUTHOR CONTRIBUTIONS

LM, and ES conceptualized the study. LM and SMR ran the analysis with contributions from ES. LM wrote the original draft of the manuscript. ES and SR supervised all study procedures. All authors reviewed, edited, and approved the manuscript.

DISCLOSURE STATEMENT

Simone Rossi is a consultant for Neurocare Italy and EBNeuro Italy. All the other authors report no conflict of interest.

**METHODS:** Selected studies, following the PRISMA guidelines, were analyzed through the Activation Likelihood Estimate (ALE) statistical framework, with subsequent generation of disorder-specific N-back activation maps.

**RESULTS:** Despite similar WM deficits shared across all disorders, results highlighted different brain activation patterns for each disorder compared to healthy controls. In general, results showed brain activity in frontal, parietal, subcortical, and cerebellar regions; however, reduced engagement of specific nodes of the fronto-parietal network emerged in patients compared to healthy controls. In particular, neither bipolar nor depressive disorders showed detectable activations in the dorsolateral prefrontal cortices, while their parietal activation patterns were lateralized to the left and right hemispheres, respectively. On the other hand, patients with ADHD showed a lack of activation in the left parietal lobe, whereas schizophrenia patients showed lower activity over the left prefrontal cortex.

**CONCLUSION:** Results, together with biophysical modeling, were then used to discuss the design of future disorder-specific cognitive enhancement interventions based on non-invasive brain stimulation.

### Keywords

ADHD; ALE metanalysis; Bipolar Disorder; Depressive Disorder; Schizophrenia

## 1. INTRODUCTION

Working Memory (WM) is the ability to temporarily keep and manipulate relevant information over brief periods of time (1,2). WM plays an important role in many forms of complex cognitive functions such as learning, abstract reasoning, problem-solving, and language comprehension, each one constantly permeating our daily life. The investigation of WM neural substrates is of great interest for several reasons, spanning from providing insight into WM processing and brain information flow dynamics to identifying novel cognitive rehabilitation strategies. Besides neurodegenerative diseases (that are not considered here), deterioration of WM capacity permeates many psychiatric disorders, such as, for example, Schizophrenia (3–5), Bipolar (6,7), and Depressive Disorders (8), as well as neurodevelopmental disorders, such as Attention Deficit Hyperactivity Disorder (ADHD) (9). Therefore, studying the neural substrates of WM has become crucial in both healthy subjects and patients in order to identify overlap and/or differences that would guide the tailoring of pathology—specific cognitive interventions aimed at restoring WM capacity.

A recent meta-analysis examining functional magnetic resonance imaging (fMRI) activity in patients with ADHD (10) showed that during three different cognitive tasks (i.e., Go/No-go, N-back, and Stroop task), patients exhibited a significantly diminished activity in the frontal lobe compared to healthy controls. However, the authors did not find significant differences in the dorsolateral prefrontal cortex (DLPFC) activation between the experimental and the healthy control groups, replicating the results previously reported during an inhibition task (11). On the other hand, an altered activity in DLPFC has been explicitly demonstrated in patients with bipolar and schizophrenic disorders compared to healthy controls, which is usually associated with a functional deficit of the anterior part of the cingulate cortex

(ACC) and thalamus (12). Thus, this lower functional connectivity between ACC and thalamus could be the neural substrate of several deficits in attention, memory, and executive functions typically associated with psychiatric disorders (6,12–14).

Tasks engaging WM typically require participants to hold and manipulate temporary information (1,15). The N-back task, first described by Kirchner (16), is the most popular measure of WM used in fMRI studies relying on the presentation of "rapidly, continuously changing information" to measure very short-term maintenance. During task performance, participants have to monitor a series of stimuli and indicate when the stimulus currently presented is the same as the one that has appeared n times before (i.e., 1-, 2-, and 3-back): the higher the number of items the subject has to hold in mind, the higher the memory load. It can be affirmed that the N-back paradigm requires several WM operations, including maintenance, monitoring, updating, and manipulation of retained information (17), therefore being the most complete task to capture WM neural substrates. Moreover, the N-back task is commonly used to assess WM capacity in pathological conditions due to its flexibility to different presentation modalities (visual or auditory), stimuli (letters, numbers, images, etc..), and load (1, 2, 3 N-back), which allows to set the task complexity based on patients' efforts and circumvent learning effects.

The neural correlates of the N-back task in healthy subjects are well characterized, as recently reviewed in a meta-analysis (18): the resulting Activation Likelihood Estimate (ALE) maps showed bilateral fronto-parietal activations, as well as concurrent activation in the bilateral insula, the bilateral cerebellum, and the precuneus. Considering the clinical population, meta-analyses showing neural correlates of different WM tasks have been already published (10,19–21), but no studies have investigated the brain activity during the N-back task specifically.

In an attempt to provide an overview of the neural correlates of N-back performance in patients with psychiatric or neurodevelopment disorders, we present a systematic quantitative meta-analysis of fMRI and PET data collected during N-back processing. This allows us to study similarities and differences in brain activity during the N-back task across psychiatric and neurodevelopmental disorders, as well as between disorders and healthy controls. Separate meta-analytic maps were created for patients with Schizophrenia (SZ), Depressive Disorder (DD), Bipolar Disorder (BD), and ADHD, showing the main activation effects of the N-back task. Furthermore, two additional maps were presented showing the simultaneous activation of brain regions involved in N-back tasks combining two psychotic disorders (SCZ and BD) and mood disorder (BD and DD). These additional maps mainly helped increase the power of our results. Moreover, we also considered the importance of presenting them because the simultaneous occurrence of multiple pathological conditions in the form of comorbidity is typical in psychiatric patients (22). Based on the previous sparse literature, we expected a decreased activation in the DLPFC in all psychiatric disorders and a less extensive activation in nodes of the fronto-parietal network in patients compared to healthy controls (23–25). Moreover, considering that depressive and bipolar disorders are both mood disorders and some studies have already shown a degree of similarity in their resting-state functional connectivity patterns, especially in the fronto-limbic network (26), we hypothesized a similar pattern of activation for these two maps. Additionally, we

investigated the qualitative overlap, thus without any statistical comparison, between these activation maps and the previously published ALE maps in healthy subjects (18), underlying similarities and differences between pathological and healthy brains in the WM domain, and suggesting possible targets for future non-invasive brain stimulation (NIBS) studies. For instance, such maps could be used to define targets for rehabilitation and cognitive enhancement purposes using Transcranial Magnetic Stimulation (TMS) and transcranial Electrical Stimulation (tES), the two techniques able to modulate one or more brain regions with an excellent spatial resolution and minimal side effects (27–32). Considering the relevance of WM to high cognitive functions, its enhancement could also resonate in other cognitive domains, such as, for example, inhibition, flexibility, and fluid intelligence, and improve patients' quality of life.

## 2. MATERIAL AND METHODS

### 2.1 ALE maps computation

We collected the data starting from a literature search on Pubmed, as described in the Method section of the Supplementary Material. We then used the activation likelihood estimate (ALE) technique implemented in the GingerALE software v3.0 (www.brainmap.org) (33,34) to capture the quantitative evaluation of spatial PET and fMRI patterns. Even though the spatial and temporal resolution of fMRI exceeds that of PET, then collapsing the two modalities in one image could be considered misleading (35), here we included only 2 studies using PET, thus it was unlikely that this would have affected our results. We produced a statistical map for each pathology indicating the set of significant voxels while considering the magnitude of the effect, the number of studies, and the number of participants. However, because these maps were created including a smaller number of studies compared to the one suggested by Muller and colleagues (36), we included two maps showing regions involved in n-back tasks considering simultaneously two psychiatric diseases. Results are described in the dedicated section and presented in the Supplementary Material (Figure S2).

First, lists of coordinates were carefully checked for duplication of data across publications, in order to avoid artefactual inflation of a given foci significance. Differences in coordinate spaces (MNI *vs.* Talairach space) between studies were accounted for by transforming coordinates reported in Talairach space into MNI coordinates through the tal2mni algorithm implemented in GingerALE. The reported foci of activation for each study were modeled as Gaussian distributions and merged into a single 3D volume. Equally-weighted coordinates were used to form an estimate of the probability of activation for each voxel in the brain, using an estimation of the inter-subject and inter-study variability usually observed in neuroimaging experiments, rather than applying a priori a full-width half maximum (FWHM) kernel. The number of participants in each study influenced the spatial extent of the Gaussian function used with this approach. Firstly, we modeled the activation probability of each spatial point in the brain overall studies, returning localized "activation likelihood estimates" or ALE values. Values were then compared to a null distribution created from simulated datasets with randomly placed foci to identify significantly activated clusters (permutations test = 1000 run). Corrections based on the false-discovery rate (FDR) at

the cluster-level and voxel-level family-wise error (FWE) estimation (34) were applied. In detail, we set cluster correction for multiple comparisons with a $p<0.001$ threshold for cluster-formation and a $p<0.05$ for cluster-level inference. All values were chosen based on their common use in similar meta-analyses and algorithm tests (34,37). Through GingerALE we also controlled that the resulting clusters for all maps were not driven by a single study, especially for the maps that included a small number of studies.

### 2.2 Qualitative meta-analysis comparison

Data acquired from our previously published ALE maps in healthy subjects (18) have been used for the current meta-analysis in order to compare healthy and pathological brain activity during the N-back task. Even though the available ALE database involved 10 maps (e.g., maps based on stimuli or presentation modality used during the N-back task), here we focused on the identification of a more general overlap between healthy and pathological subjects, without considering specific stimulus or presentation modality, therefore we used the general map (corresponding to the data shown in Figure 1 and Table 1 in (18)). The results from this comparison should be evaluated carefully considering the differences in sample size used for different maps.

### 2.3 Biophysical modeling

The definition of possible targets for future NIBS studies with rehabilitation and cognitive enhancement purposes has been detected using customized biophysical modeling. We propose different examples of how to use specific ALE maps for targeting both TMS and more advanced tES multielectrode solutions optimized by software. More details are described in the Supplementary Material.

## 3. RESULTS

### 3.1 N-back task activation profile in Schizophrenia

Figure 1 and Table 1 show the resulting maps and coordinates of the comprehensive set of activity patterns in patients with SZ (mean age: 31,6) during the execution of the N-back task. The map includes 8 separate nodes showing a right fronto-parietal distribution of activation. Moreover, there are additional contributions of regions in the left cerebellum, left superior parietal lobule, and temporal structures including the fusiform gyrus (Figure 1A). A qualitative overlap between brain activity during the N-back task in SZ patients and healthy subjects (as shown in (18)) is reported in Figure 1B.

### 3.2 Activation patterns in Depressive Disorder

Figure 2 and Table 2 report neural activation patterns during N-back tasks in patients with DD (mean age: 36,6). The map includes 5 clusters (i.e., nodes) of activation highlighting an involvement of the bilateral frontal cortices, the right parietal cortex, and the middle temporal gyrus. All studies included in this analysis used verbal stimuli (numbers or letters) in the N-back task. A qualitative overlap between brain activity during the N-back task in DD and healthy subjects (as shown in (18)) is depicted in Figure 2B.

### 3.3 Activation patterns in Bipolar Disorder

Figure 3 and Table 3 show the maps and coordinates of activity patterns elicited during the performance of the N-back tasks in patients with BD (mean age: 41,9). The map includes 3 clusters (i.e., nodes) of activation showing left lateralization of activation in the fronto-parietal areas and the subcortical structure (i.e., the lentiform nucleus). All studies included in this analysis used letters as stimuli in the N-back task. A qualitative overlap between brain activity during the N-back task in BD and healthy subjects (as shown in (18) is reported in Figure 3B.

### 3.4 Activation patterns in ADHD

Figure 4 and Table 4 report brain activity in patients with ADHD (mean age: 20,9) during N-back tasks and their corresponding set of coordinates. The map includes 7 clusters (i.e., nodes) of activation highlighting a bilateral involvement of the frontal areas, the right parietal areas, as well as the right subcortical structures, and the right cerebellum. No active nodes were found over temporal regions. A qualitative overlap between brain activity during the N-back task in patients with ADHD and healthy subjects (as shown in (18) is illustrated in Figure 4B.

### 3.5 N-back task activation profile in psychosis and mood disorders

Figure S2 A and Table S2 (reported in the Supplementary Material) show the resulting maps and coordinates of the comprehensive set of activity patterns in patients with SZ and BD during the execution of the N-back task. The map includes 7 clusters showing a bilateral fronto-parietal distribution of activation. (Figure S2 A).

Additionally, considering together the mood disorders (BD and DD), a bilateral activation of parietal areas, as well as a more lateralized activation of frontal areas, are shown. A small contribution of the right temporal cortex is also presented (Figure S2 B; Table S3).

### 3.6 Functional overlap between the different disorders and healthy subjects

The resulting overlap for the overall pattern of activation during N-back tasks in four considered disorders and healthy subjects is reported in Figure 5. Because the resulting patients' maps could have been influenced by some biases, as for example medication, and because we could not have controlled for these biases, we did not perform any statistical analysis comparing diseases to healthy controls. Therefore, we only show the qualitative overlap between the resulting cluster of activations of each map.

Figure 5 highlights the involvement of the left cerebellum as well as of the right frontal cortex only for ADHD and Schizophrenia, whereas the involvement of subcortical structures is especially marked in ADHD. Bilateral activation of parietal areas is more visible in patients with Schizophrenia. Conversely, patients with other disorders showed lateralization in right (ADHD and DD) or left (BD) parietal regions. All these pieces of evidence overlap with the healthy subject map (in yellow). However, activity in the right subcortical areas (e.g., claustrum, caudate) as well as in the right cerebellum and insula is specifically shown in healthy people and none of the other pathological groups considered. Temporal activation on the left hemisphere is also typically observed in healthy subjects, whereas SZ and DD

patients have a similar contribution only on the right temporal cortex. On the other hand, BD and ADHD did not show any temporal activation during the N-back task. Considering the bilateral parietal and frontal areas, neural activations are spatially similar between healthy and pathological cohorts, but they are wider in healthy subjects.

### 3.7 Biophysical Modeling Results

The results of this meta-analysis located the most relevant regions of increased functional connectivity during the performance of the N-back task in psychiatric and neurodevelopmental disorders. Therefore, they provide relevant details to inform future targeted NIBS interventions aimed to improve WM performance in the different clinical cohorts, as summarized in Figure 6. In particular, we suggest two possible approaches: (i) restoring missing activations, thus appropriately stimulating regions (i.e., nodes) that are activated in healthy subjects but not in the clinical cohort; (ii) boosting the existing activations, thus upregulating regions (i.e., nodes) still active during the N-back task in patients. Following the latter approach, we also computed biophysical modeling and computational simulations of TMS and tES paradigms to obtain the optimal NIBS montages targeting the main clusters involved during the N-back task performance in the clinical cohorts considered. In particular, considering the resulting ALE maps, we decided to propose a TMS solution targeting the cluster on the parietal lobe, the only one directly reachable by TMS, for depressive disorder. On the other hand, the tES multielectrode solutions are proposed for patients with Schizophrenia, Bipolar Disorder, and ADHD. These three ALE maps present two or three cortical clusters, thus making them the optimal examples to compute the multielectrode optimization. However, these should be considered only as NIBS examples since montages need to be optimized based on specific tES/TMS devices and requirements. Moreover, empirical data supporting that those protocols are effective are needed.

Figure 7 reports the results of TMS simulation and tES multielectrode optimizations promoting the activation of the regions still active during the N-back task in the cohort of patients considered. We performed four different optimizations, one for each clinical group, offering an overview of how ALE maps can drive the biophysical modeling. In this case, the stimulation targets have been selected based on both the higher extrema values as reported by GingerALE maps (see the corresponding tables for each coordinate) and on clinical experience. For example, we excluded the clusters not directly reachable by NIBS (as in the case of the subcortical clusters shown in the resulting ALE map for patients with depression), or we restricted the optimization to the two or three more representative clusters (as in the case of ADHD and Schizophrenia maps). The weighted maps used for the four optimizations are shown in Figure 7 (on the top of panels A-D), as well as the TMS simulation for DD (Figure 7A), and multielectrode tES optimizations for BD, SZ, and ADHD (Figure 7 B, C & D). However, these are not the only solutions available, because several and specific analyses can be run, and, in practice, all the solutions can be optimized based on the well-suited stimulation method. Details about the E-field and the TMS/ tES montages obtained are included in the Supplementary Materials.

# 4. DISCUSSION

We showed a set of specific maps representing the neural substrates of the N-back task in patients with SZ, DD, BD, and ADHD. Moreover, we also presented less specific maps, observing that the ALE maps obtained with a higher number of papers are similar to the less powerful maps. In the following paragraphs, we will discuss the functional role of the resulting core regions (or nodes) for each examined disorder, as well as the observed overlap with maps previously computed in healthy subjects (18). Finally, we will discuss the utility of different activation patterns for planning neuromodulation and cognitive enhancement interventions, as described in Figures 6 and 7.

## 4.1 Core Regions in Schizophrenia

Frontal hypoactivation during cognitive training in SZ patients, compared to healthy subjects, has been consistently observed in the literature (20,24) as well as the functional connectivity alteration in the fronto-temporal (38), default mode (39), and fronto-parietal networks (40,41). Particularly, the bilateral fronto-parietal networks have been implicated in the N-back task in healthy subjects (18), and the lack of neural activity in this network in SZ patients has been usually linked to their lower performances in WM tasks. Nevertheless, the ALE map resulting from the present study shows a neural activity pattern similar to control subjects (as shown in Figure 1B). The fronto-parietal network is activated during the N-back task even in SZ patients, although with strong lateralization to the right hemisphere. Therefore, differently from the previous meta-analyses on SZ patients (20,24), we find activations also in the frontal lobe, even if reduced when compared to healthy controls.

The activation found in the left cerebellum may be considered an unexpected result because it was not previously described in former meta-analyses (20,24) and neither in the ALE map built considering together psychosis (SZ and BD; Figure S2 A), even though it is in line with activity related to the N-back task in healthy subjects. Indeed, as previously explained by Marvel and Desmond (42), WM tasks could be supported by the cerebellum through the engagement of the inner speech mechanism. Moreover, the development of inhibitory control seems to be mediated by the functional maturation of fronto-cerebellar neural pathways (43). This, together with the hypothesis that only the inferior frontal gyrus (IFG) could be specialized for the interplay with cerebellar areas for inhibitory control (44), could support the role of the cerebellum in SZ patients while performing the N-back task and also in other cognitive functions.

Finally, Glahn and colleagues (2005) underlined increased activation in the anterior cingulate cortex (ACC) and left frontal pole regions in SZ patients during the N-back task. The authors suggested that abnormal activation patterns are not restricted to the DLPFC, despite reduced activation of this region consistently reported in SZ patients (24). However, our results are not in line with their observations because we did not find activity in the ACC. The hypothesis that ACC activity increases during the cognitive task in SZ patients due to hypoactive frontal areas cannot be supported by our results, which, as matter of fact, revealed the opposite. Our findings partly sustain the guided activation model formulated by Miller and Cohen (45). This model affirms that the concurrent activation of DLPFC and ACC is needed for the right allocation of additional control during a task. In SZ patients,

the absence of activity in ACC during a task that requires sustained attentional control (i.e., N-back task) may be the cause of their poor WM performance, as well as the general cognitive impairment in many daily life activities.

### 4.2 N-back and Depressive Disorder

Several neuroimaging studies have been conducted while patients with DD were performing WM paradigms, showing that their WM impairments could be mediated by the aberrant activity in related brain areas such as the prefrontal, parietal, temporal, cerebellar, and subcortical regions (46–48). However, these studies reported contrasting findings: some studies described increased activation of the DLPFC and/or ventrolateral prefrontal cortex (VLPFC) in patients compared to controls (46,48,49), while others observed decreased activity in the same areas (50–52); additionally, null findings have also been shown from other studies (53–55). These discrepancies may be due to the different nature of the subjects included: for example, some studies included patients on antidepressant medication, whereas other studies considered only patients not treated with medication or other therapies (e.g., Electroconvulsive Therapy- ECT). Moreover, recent meta-analyses also showed heterogenic results, probably because they merged cognitive and emotional experiments, while others focused only on one specific aspect (21,56), and also our results stand back to the previous findings.

Our results showed an involvement of the left and right medial frontal gyri and of the right parietal and temporal areas that have been already reported as involved in the N-back paradigm in healthy controls (18) (Figure 2B). The inferior parietal cortex (BA 40) and the angular gyrus (BA39) play an important role in maintaining temporal information and switching attention rapidly (57), as well as in preparing for a forthcoming given task (58). Differently from Wang and colleagues (2015), we did not find a specific prefrontal hyperactivation during WM processing in the left DLPFC and VLPFC (56). However, as we focused our meta-analysis on a single WM task (N-back), different results from other meta-analyses were expected. In particular, the lack of activation in the bilateral DLPFC during the N-back task may be associated with local hypometabolism (59,60) and decreased Cerebral Blood Flow (CBF) (61,62) usually reported in patients with DD when compared to controls. However, some studies suggested that a good WM performance in patients with DD is associated with increased cortical activity, while impaired performance is associated with a decrease in cortical activation (63,64). Even though this represents a crucial aspect of clinical trials, we could not investigate it in our study due to the insufficient number of studies collected.

### 4.3 Core regions in Bipolar Disorder

Several studies have demonstrated that cognitive impairment, involving executive functions and long-term memory (65), is a common feature in patients with BD. Recent neuroimaging studies provided abundant evidence for brain functional correlates of cognitive deficits in BD. Focusing on WM deficits, they have shown an aberrant activity in the prefrontal, parietal, and temporal cortices during WM tasks. However, in this case, the available specific literature is not extensive, and the results are moderately heterogeneous: all the studies presented a mixed picture of hyperactivation and hypoactivation in the brain regions that

are traditionally involved in WM circuits, including the DLPFC, the VLPFC, as well as the parietal and temporal cortices (66–69). However, our results, which are focused on the N-back task only, showed a parietal as well as a subcortical activation, in line with the neural pattern showed by Mencarelli et al., (2019) in healthy subjects, even though with less extensive activity in BD. Unexpectedly, we found left hemisphere lateralization in BD, which has not been reported previously. This inconsistency could be the result of the balance between homogeneity and robustness: in this work, we decided to focus on brain activity in BD during the N-back task, complying with the criteria of homogeneity but, due to the limited literature available so far, we did not completely observe the criteria for robustness (36). Nevertheless, this evidence should be interpreted carefully since the results of a meta-analysis with a low number of papers could be driven by few experiments (70). In fact, looking at the results obtained considering simultaneously mood disorders (Figure S2 B) this parietal lateralization in BD is lost, given the bilateral activation in the parietal cortex. Whereas, the lack of activity in the frontal cortices is remarked. Moreover, other potential confounding factors, such as different pharmacological treatments and clinical variables used across the considered studies, could also have driven the results.

Additionally, as hypothesized, both BD and DD did not show activation in DLPFC. Several neuroimaging evidence has shown a similar pattern of brain abnormalities for mood disorders, with the involvement of the prefrontal cortex, the limbic system (e.g. the amygdala), the ventral striatum, the insula, and the hippocampus (71–74). This has also been confirmed by other neuroimaging modalities, underlining, for example, that DD and BD are characterized by abnormalities in white matter tracts of the genu of the corpus callosum that connect the prefrontal cortices of the two hemispheres implicated in mood regulation (75). However, looking at the parietal activation, the two mood disorders showed an opposite pattern, even though all the studies considered utilized a verbal N-back task, thus using the letters and/or numbers as stimuli: lateralization on the left hemisphere has been shown for BD, whereas lateralization on the right hemisphere has been found for DD. These findings may support the idea that failure to engage bilateral fronto-parietal network in mood disorders could represent the core substrate of cognitive impairment; this hypothesis should be verified in future studies.

### 4.4 Brain activity in patients with ADHD

The main behavioral features in ADHD are inattention and impulsivity, which, as a collateral effect, lead to executive function impairment. To understand whether this impairment could be directly linked to functional changes within specific brain regions, several studies have run WM tasks during fMRI in patients with ADHD. The current meta-analysis gathers all these studies to create a comprehensive activation map for the N-back task. As in healthy subjects (as shown in Figure 4B), results in ADHD showed brain activity in frontal, parietal, subcortical, and cerebellar regions (Figure 4A), although generally reduced. This result is in line with the literature in the field: several studies have already pointed out that participants with ADHD displayed hypoactivity compared to healthy controls in the right superior and middle frontal areas as well as in cerebellar, occipital, and parietal areas (10,76–79). Moreover, differently from healthy controls, there is no activation in the left DLPFC and left parietal regions in patients with ADHD. The anomalous activity in the former was shown

in a previous meta-analysis (10), and this is expected since DLPFC plays an important role in monitoring and updating the incoming information (80–84), skills known to be impaired in ADHD. However, the dysfunctional activity in the left parietal cortex has never been pointed out in this clinical cohort. This area is involved in many higher-order functions, particularly in the maintenance of goal-directed attention (85), and has an important role in the N-back task (18). However, the direct comparison between the neural activation in healthy subjects and patients with ADHD should be interpreted carefully due to sample differences: in Mencarelli et al. (2019), all the N-back studies performed on children have been excluded; while in the present meta-analysis, also studies that considered children or young adults in the sample have been included, as ADHD is a neurodevelopmental disorder. Moreover, some neuroimaging studies have considered patients with ADHD as a whole group without differentiating between patients with and without working memory deficits, whereas other studies considered this difference. These latter studies highlighted that the impairment in the fronto-parietal network is mostly shown in patients with WM deficits (78). Unfortunately, the small number of studies available did not allow us to investigate if there is a direct link between the similarity in brain activation patterns between patients with ADHD and healthy controls and WM performance.

### 4.5 Potential NIBS targets for Cognitive Enhancement

The present results shed light on the common and specific neural basis of the N-back task in psychiatric and neurodevelopmental populations and might suggest potential targets for TMS and tES neuromodulatory interventions (30,31,86). Several non-invasive therapeutic applications have been proposed so far but with inconsistent results. In a recent review, Hill and colleagues showed that anodal tDCS applied to a clinical population significantly improves accuracy for online but not offline WM tasks, and no effect was found on the reaction times (87). The heterogeneity between studies could be ascribed to several factors, such as, for example, current density and stimulation duration, but also to the stimulation target. Most studies investigating the effects of NIBS on WM performance have targeted the DLPFC due to its strong involvement in WM tasks (for a comprehensive review, see (85)). However, there are several WM tasks, and not all of them have the same neural substrate (e.g., backward digit span, dual-task, visual pattern recall, visual working memory task; 87–89); also, subjects' age may play a role in the responsiveness to NIBS for WM tasks, with the younger subjects reacting better than the older ones (92). Moreover, better results in terms of cognitive enhancement could be obtained using the fMRI-guided targeting for NIBS, increasing the accuracy of the targeting of the brain region of interest.

Considering the N-back task, several brain regions are recruited when the task is performed by healthy subjects, including frontal, parietal, and cerebellar areas (18,84,93); however, DLPFC has been the most commonly used target to boost N-back performance by NIBS, so far. Nevertheless, given the activation maps presented in this study, this brain region might not be the best target for patients with WM deficits: the ideal parameters in one population may not be optimal in another. For instance, our results showed that patients with schizophrenia mostly activate the right fronto-parietal network and the left parietal cortex, whereas less activity has been shown in the left frontal cortex; on the other hand, patients with DD showed activation mostly in the right parietal cortex. In this case, the choice of

the stimulation target must be based on the patients' brain activity when a neuromodulation intervention is planned. Following our results, the possible approaches may aim to (i) improve the activity of nodes still active even in the presence of a pathological condition and WM deficit, or (ii) reactivate nodes of the N-back network showing a lack or reduction of activation as compared to healthy controls (Figure 6). Considering the first option, we used biophysical modeling and proposed the most optimal target for different NIBS approaches (TMS and multielectrode tES) based on each generated ALE map (Figure 7). Future studies may investigate the effects of stimulation over these locations, covering additional therapeutic targets that have never been considered so far, such as, for example, the parietal and temporal cortices. Moreover, only single-site stimulation has been tested in patients with WM deficits to date, except for a recent study based on tACS in elderly subjects aimed to synchronize brain oscillatory activity in frontotemporal networks (94). However, it is unlikely that the single-site stimulation approach will produce a clinically meaningful whole-brain effect, and corresponding cognitive effects could be inconsistent between studies, as already pointed out in recent reviews (85,93). Recently, multielectrode stimulation devices have been developed, allowing the stimulation delivery over multiple cortical sites using small and more focal electrodes (96). These devices could provide an innovative alternative for potentially stimulating the entire WM network or functional MRI networks, as suggested in Figures 7 B, C & D and already proved in healthy (97–101) and clinical (102–104) cohorts. Moreover, future studies could analyze the functional connectivity profile of the ALE regions reported in our meta-analysis, suggesting the hypoactivation/hyperactivation of one or more networks in the clinical cohort and leading to a more specific non-invasive brain stimulation intervention. The level of personalization proposed here, however, is not the only one available: the protocols could also be personalized in terms of TMS-tES parameters, such as, for example, stimulation intensity and the number of TMS pulses as well as the number of stimulation sessions. The NIBS approach proposed here, indeed, needs further clinical investigation, considering that an increase in WM function would not automatically transfer to another executive function nor would directly lead to clinical improvement.

Future studies could also consider the use of other techniques, such as EEG as well as TMS-EEG, to explore brain-behavior relationships (105–108), provide more information on the temporal dynamics between networks, and characterize network-level individual brain dynamics (109) useful for NIBS interventions (e.g., cc-PAS TMS, 107–111).

Finally, NIBS interventions are not the only ones useful for increasing WM performance in patients with cognitive deficits. Several studies have already pointed out that specific memory training programs produce short-term effects but, unfortunately, do not generalize to other cognitive domains (for a comprehensive review, see (115)). Other studies reported the possibility of increasing WM capacity through mindfulness meditation (116,117) or physical exercises (118–120), but with inconsistent results. Moreover, evidence suggests that combining two kinds of interventions, cognitive training and physical activity training, improves cognitive function in healthy older adults (for a comprehensive review, see (121)). From this perspective, the combination of NIBS with cognitive interventions offers a potentially powerful new approach to treating neuropsychiatric disorders, as recently reviewed by Sathappan and colleagues (122). In this case, the timing of the NIBS is

important since it could be applied online or offline for cognitive intervention. In particular, the functional engagement of a specific network during a cognitive task could simplify the long-term potentiation effects obtained with neuromodulation. Future studies could demonstrate the efficacy of WM training combined with MRI-guided targeted NIBS based on different clinical cohorts.

### 4.6 Limitations of the study

The aim of this study was to show brain activation patterns typically involved in patients with WM deficit while performing the n-back task, suggesting possible personalized targets for future NIBS protocols aiming at cognitive enhancement. Even though we consider our results a very accurate representation of available literature, potential biases should be accounted for. A recent paper from Muller and colleagues (36) pointed out the importance of considering the right balance between homogeneity and power while performing a quantitative meta-analysis. In our study, due to the small number of papers available for each disease, we did not observe the suggestion of at least 17 experiments for each ALE map (36) when we considered the disorders separately. At the same time, the ALE maps considering together two psychiatric disorders (SCZ & BD; BD & DD; Figure S2) have accomplished the power, and still, the results are similar to those presented in the separate maps. Additionally, we controlled that every resulting map was not driven by a single study, a typical issue when a small number of studies is included in a meta-analysis. Moreover, focusing on a specific task (and, therefore, a smaller number of studies) is also important to provide specific contributions to the field of interest, thus accounting for the homogeneity between the studies included.

Furthermore, the results showing the overlap between healthy subjects and patients' ALE maps should be evaluated carefully because no statistical comparison has been performed between these maps. Considering the differences in sample size used as well as other potential confounding factors (e.g., different pharmacological treatments), we settle for a qualitative overlap between maps.

## 5. CONCLUSIONS

The present work reveals similarities and differences in brain activity within SZ, DD, BD, and ADHD during the N-back task and offers a disorder-matched comparison to neural activations in healthy controls, suggesting the new potential targets for personalized NIBS interventions. The results encourage the fMRI-guided montage stimulation and hint at potential avenues to enhance WM in clinical cohorts, with an emphasis on other brain regions instead of the commonly used target in the DLPFC.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## DATA AVAILABILITY

The results of ALE maps will be available for download as a volumetric file (.nii) at www.tmslab.org/santalab.php

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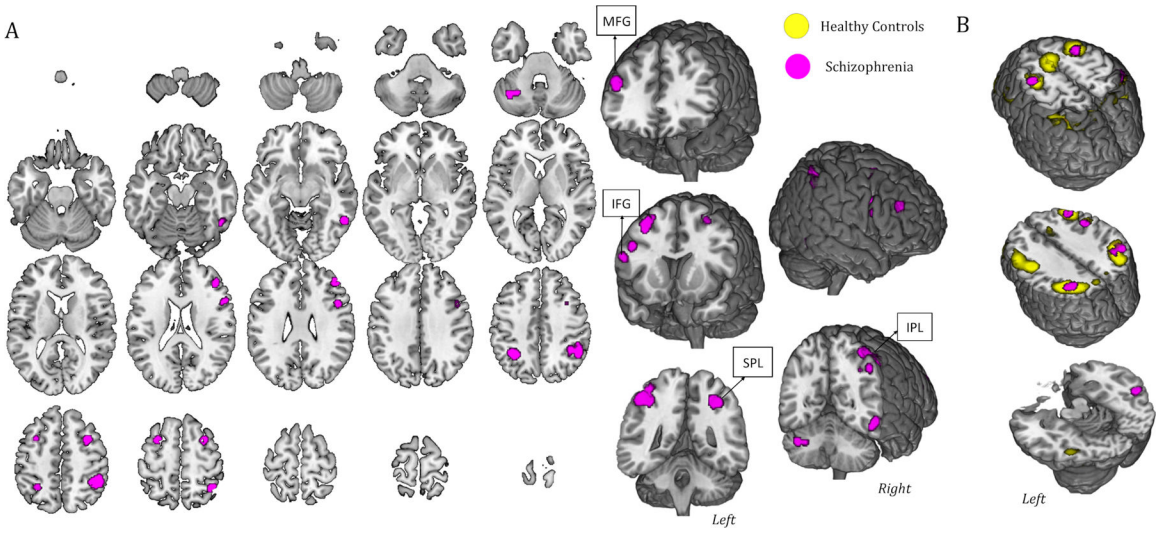


**Figure 1. Activation maps of the N-back task in Schizophrenia.**

(A) The map refers to 13 studies in which the N-back task was performed by patients with schizophrenia (SZ). A complete set of coordinates for each cluster is available in Table 1. (B) Some significant slides of the brain activation overlap between healthy subjects (yellow) and SZ patients (pink) are shown. Note: MFG: Middle Frontal Gyrus; IFG: Inferior Frontal Gyrus; SPL: Superior Parietal Lobule; IPL: Inferior Parietal Lobule.

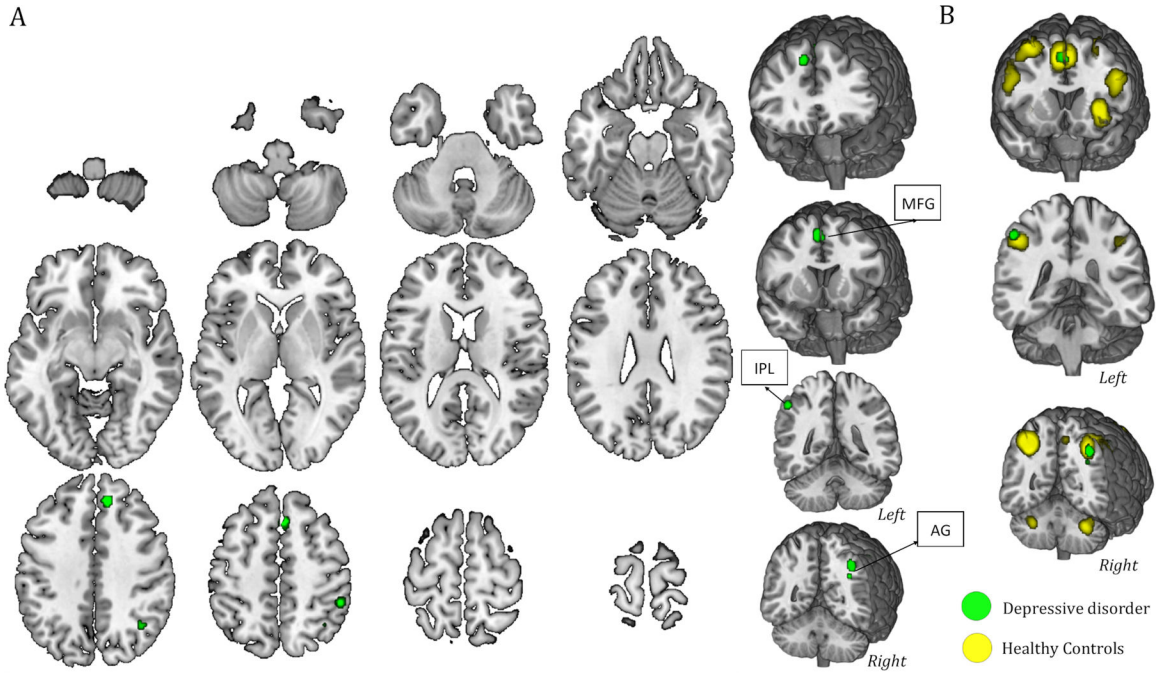


**Figure 2. Activation maps of the N-back task in Depressive Disorder.**

(A) The map refers to 10 studies that analyzed neural substrates during the N-back task in patients with depressive disorder. A complete set of coordinates for each cluster is available in Table 2. (B) Qualitative overlap with the healthy subjects' map (in yellow) is presented. Note: MFG: Middle Frontal Gyrus; IPL: Inferior Parietal Lobule; AG: Angular Gyrus.

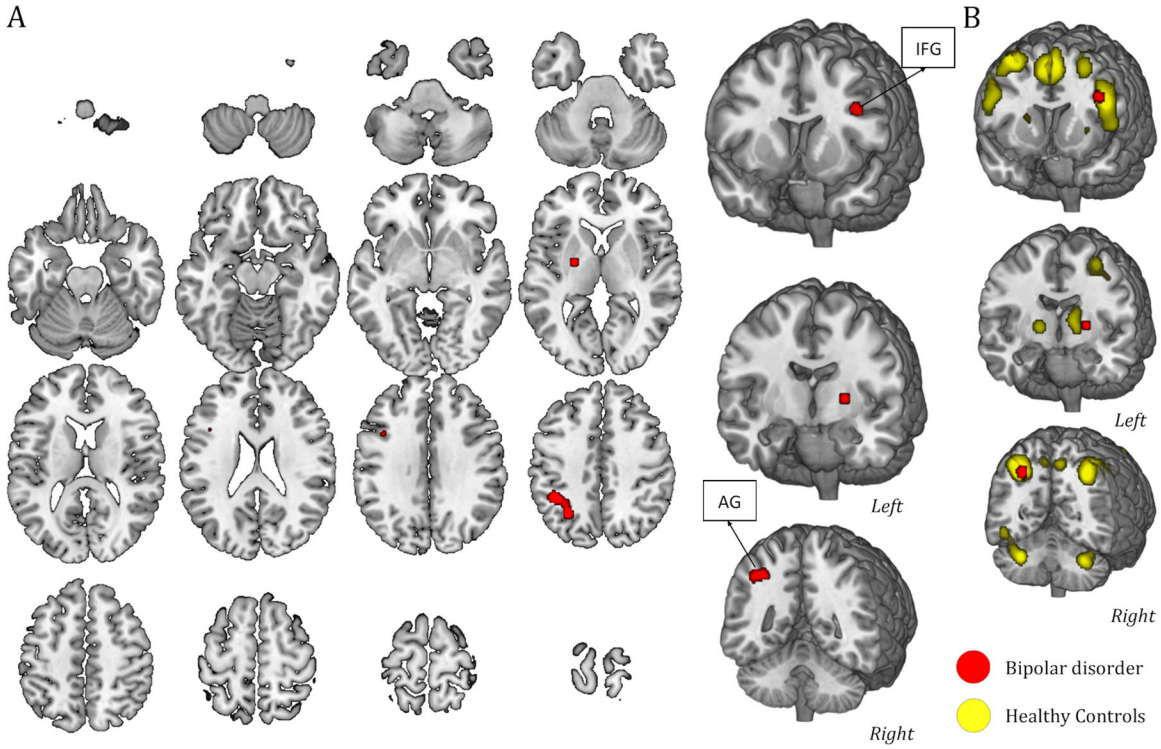


**Figure 3. Activation maps of the N-back task in Bipolar Disorder.**

(A) The map refers to 8 studies in which the N-back task was performed by patients with bipolar disorder. A complete set of coordinates for each cluster is available in Table 3. (B) Significant slides of the qualitative overlap with the healthy subjects' map (in yellow) are reported. Note: IFG: Inferior Frontal Gyrus; AG: Angular Gyrus.

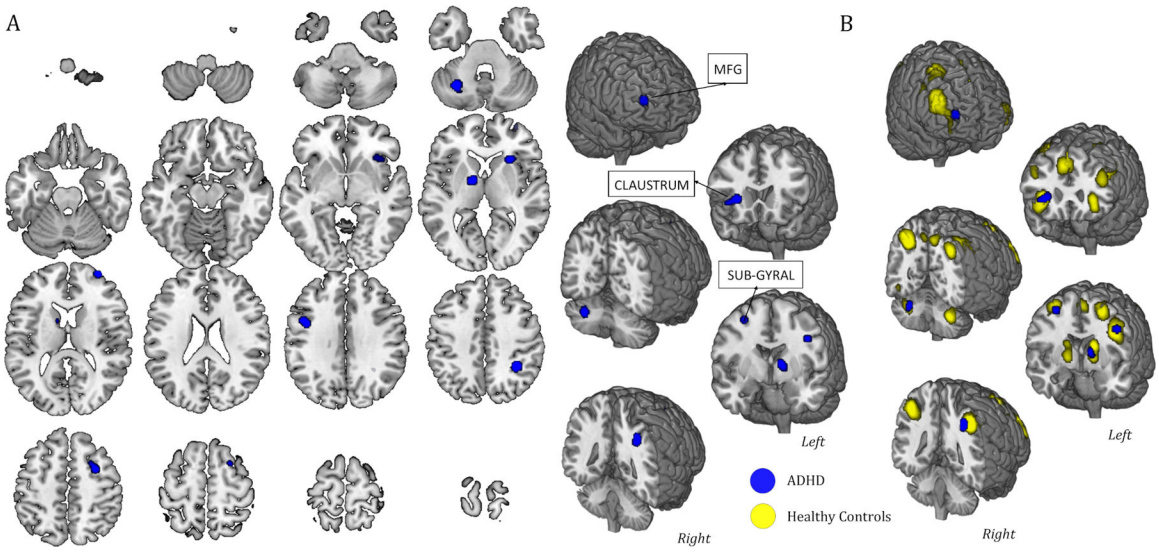


**Figure 4. Activation maps of the N-back task in ADHD.**

(A) The map refers to 5 studies in which the N-back task was performed by patients with Attention Deficit Hyperactivity Disorder (ADHD). A complete set of coordinates for each cluster is available in Table 4. (B) Qualitative overlap with the healthy subjects' map (yellow) is shown. Note: MFG: Middle Frontal Gyrus.

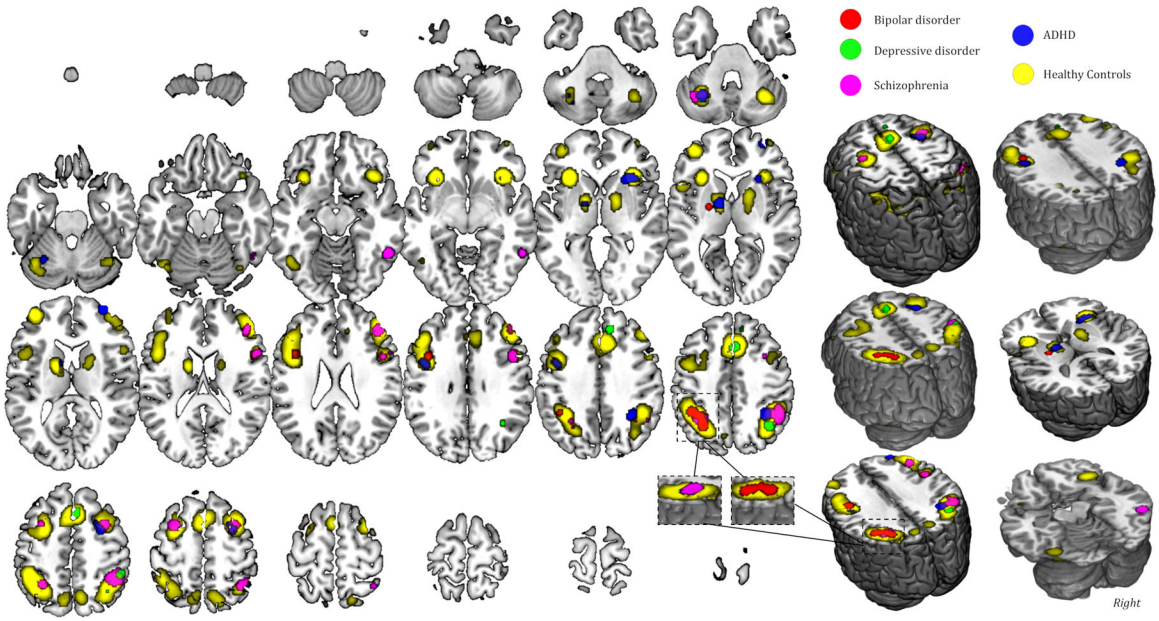


**Figure 5. Overlap between the considered disorders and healthy subjects.**

The map shows a qualitative overlap of activation during the N-back task between the four pathologies considered in this study and the general healthy map corresponding to the data shown in Figure 1 and Table 1 in (18). The map is shown on a template brain in MNI space. MNI= Montreal Neurologic Institute.

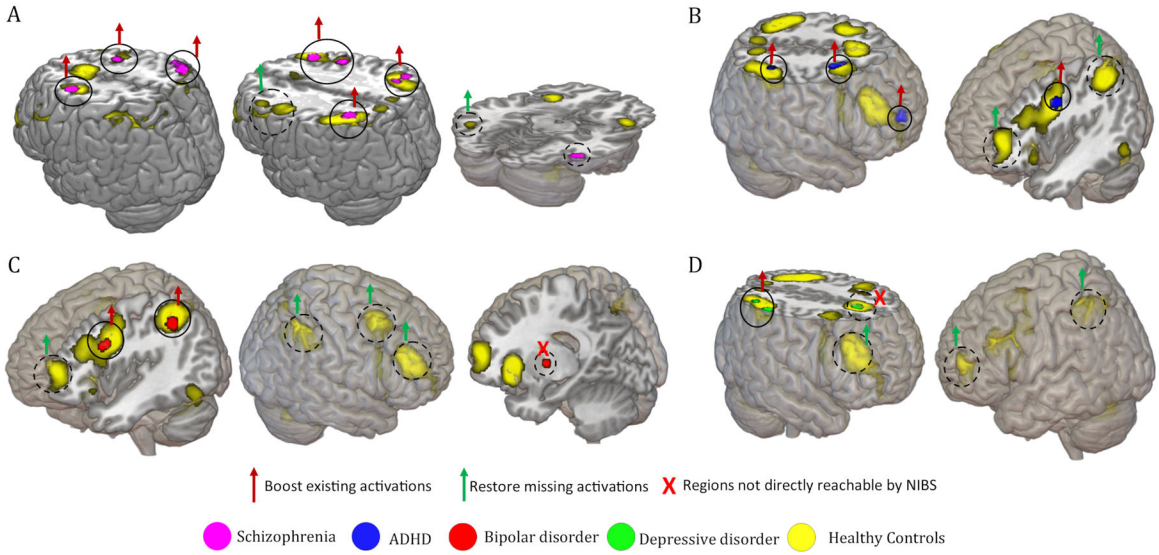


**Figure 6. Possible targets for NIBS.**

Cortical regions that could be used as targets for Non-Invasive Brain Stimulation (NIBS) are shown. Areas of overlap between healthy subjects and patients are highlighted with continuous line circles and red arrows, whereas areas that show activation only in the healthy subjects' map are underlined by dashed line circles and green arrows. Deep cortical regions and subcortical regions are depicted with an X since they are not accessible directly through NIBS. Areas of non-overlap with healthy subjects' map could be an expression of compensatory mechanisms or dysfunctional activity, future investigation should be conducted to detect the stimulation polarity (inhibitory or excitatory). (A) SZ; (B) BD; (C) ADHD; (D) DD.

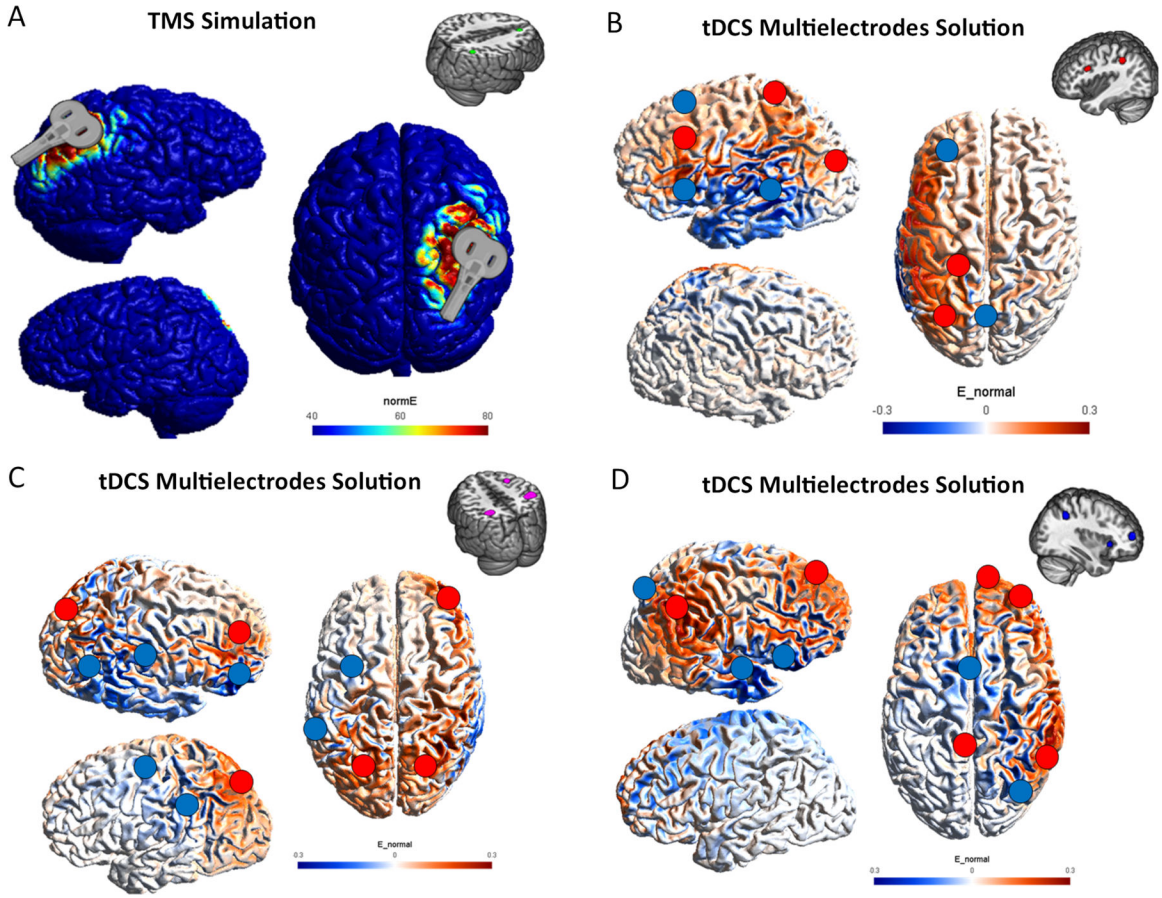


**Figure 7. Optimization montages for each clinical cohort.**

Stimulation montages aimed at boosting the nodes still active during the N-back task are proposed with different Non-Invasive Brain Stimulation (NIBS) techniques. In panel A, we suggest stimulating patients with depression disorder on the right angular gyrus through Transcranial Magnetic Stimulation (TMS), based on the ALE map. In panels B, C, and D, we propose multielectrode transcranial Electrical Stimulation (tES) solutions aimed at improving the activity on two or three nodes of the network triggered by the N-back task in patients with Schizophrenia, Bipolar Disorder, and Attention Deficit Hyperactivity Disorder. The weighted map and the E-field (V/m) for each montage are presented (NormE for TMS simulation and NormalE to show polarity for tES solutions—information about the specific montages and fields resulted are reported in the Supplementary Materials).

**Table 1.**

Pattern of activation during the N-back tasks in patients with Schizophrenia. Volume, coordinates, and corresponding Brodmann area, lobe, hemisphere, and regional labels are reported for each cluster included in the ALE map.

| Cluster number | Volume ($mm^3$) | Weighted Center | | | Extrema Value | Extrema value coordinates | | | Brodmann Area | Hemisphere | Lobe | Label |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | | *x* | *y* | *z* | | | | |
| | | | | | | | | | | | | |
| **1** | 4000 | 43.2 | −47.1 | 48.8 | 0.023 | 48 | −46 | 48 | 40 | R | Parietal | Inferior Parietal Lobule |
| | | | | | 0.022 | 38 | −52 | 58 | 7 | R | Parietal | Superior Parietal Lobule |
| | | | | | 0.021 | 40 | −46 | 48 | 40 | R | Parietal | Inferior Parietal Lobule |
| | | | | | 0.019 | 36 | −54 | 40 | 39 | R | Parietal | Angular Gyrus |
| **2** | 1552 | −32.2 | −51.5 | 44.6 | 0.023 | −30 | −52 | 46 | 7 | L | Parietal | Superior Parietal Lobule |
| **3** | 1512 | 30.9 | 7.6 | 52.8 | 0.018 | 32 | 8 | 52 | 6 | R | Frontal | Sub-Gyral |
| **4** | 1176 | 42.9 | 36.9 | 24.1 | 0.022 | 42 | 36 | 24 | 9 | R | Frontal | Middle Frontal Gyrus |
| **5** | 1152 | 48.7 | 11.6 | 26.2 | 0.019 | 46 | 10 | 30 | 9 | R | Frontal | Inferior Frontal Gyrus |
| | | | | | 0.015 | 54 | 14 | 20 | 9 | R | Frontal | Inferior Frontal Gyrus |
| **6** | 904 | 53.2 | −52.6 | −12.1 | 0.021 | 54 | −52 | −12 | 37 | R | Temporal | Fusiform Gyrus |
| **7** | 904 | −30.6 | 8.2 | 55.3 | 0.018 | −32 | 8 | 54 | 6 | L | Frontal | Middle Frontal Gyrus |
| **8** | 720 | −35.4 | −60.8 | −32.9 | 0.017 | −38 | −62 | −32 | . | L | Cerebellum | Tuber |
| | | | | | 0.014 | −28 | −60 | −34 | . | L | Cerebellum | Cerebellar Tonsil |

**Table 2.**

Pattern of activation during the N-back tasks in patients with Depressive Disorder. Volume, coordinates, and corresponding Brodmann area, lobe, hemisphere, and regional labels are reported for each cluster included in the ALE map.

| Cluster number | Volume ($mm^3$) | Weighted Center | | | Extrema Value | Extrema value coordinates | | | Brodmann Area | Hemisphere | Lobe | Label |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | | *x* | *y* | *z* | | | | |
| | | | | | | | | | | | | |
| **1** | 664 | 2.77 | 20.11 | 47.07 | 0.025 | 2 | 20 | 46 | 6 | L | Frontal | Medial Frontal Gyrus |
| **2** | 480 | 37.31 | −58.65 | 44.29 | 0.021 | 38 | −58 | 44 | 39 | R | Parietal | Angular Gyrus |
| **3** | 296 | 49.37 | −40.74 | 48.74 | 0.022 | 50 | −40 | 48 | 40 | R | Parietal | Inferior Parietal Lobule |
| **4** | 288 | 9.67 | 37.58 | 38.71 | 0.020 | 10 | 38 | 38 | 8 | R | Frontal | Medial Frontal Gyrus |
| **5** | 96 | 35.01 | −56.32 | 32.35 | 0.017 | 36 | −56 | 32 | 39 | R | Temporal | Middle Temporal Gyrus |

**Table 3.**

Pattern of activation during the N-back tasks in patients with Bipolar Disorder. Volume, coordinates, and corresponding Brodmann area, lobe, hemisphere, and regional labels are reported for each cluster included in the ALE map.

| Cluster number | Volume ($mm^3$) | Weighted Center | | | Extrema Value | Extrema value coordinates | | | Brodmann Area | Hemisphere | Lobe | Label |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | | *x* | *y* | *z* | | | | |
| | | | | | | | | | | | | |
| **1** | 1632 | −34.8 | −50.9 | 43.4 | 0.024 | −42 | −44 | 42 | 40 | L | Parietal | Supramarginal Gyrus |
| | | | | | 0.019 | −30 | −58 | 44 | 39 | L | Parietal | Angular Gyrus |
| **2** | 376 | −41.1 | 12.05 | 28.13 | 0.017 | −40 | 12 | 28 | 9 | L | Frontal | Inferior Frontal Gyrus |
| **3** | 152 | −24 | −6 | 4 | 0.018 | −24 | −6 | 4 | . | L | Sub-lobar | Lentiform Nucleus |

**Table 4.**

Pattern of activation during the N-back tasks in patients with ADHD. Volume, coordinates, and corresponding Brodmann area, lobe, hemisphere, and regional labels are reported for each cluster included in the ALE map.

| Cluster number | Volume ($mm^3$) | Weighted Center | | | Extrema Value | Extrema value coordinates | | | Brodmann Area | Hemisphere | Lobe | Label |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | | *x* | *y* | *z* | | | | |
| | | | | | | | | | | | | |
| **1** | 1112 | 33.3 | −47.1 | 41.7 | 0.020 | 34 | −46 | 42 | 7 | R | Parietal | Precuneus |
| **2** | 1040 | 29.7 | 22.1 | .4 | 0.015 | 28 | 22 | 2 | . | R | Sub-Cortical | Claustrum |
| **3** | 1032 | −30.4 | −61.1 | −32 | 0.017 | −32 | −60 | −32 | . | L | Cerebellum | . |
| **4** | 848 | 32 | 58 | 10.7 | 0.017 | 32 | 58 | 10 | 10 | R | Frontal | Middle Frontal Gyrus |
| **5** | 840 | −13.5 | −2.2 | 6 | 0.014 | −14 | −2 | 6 | . | L | Sub-Cortical | Lentiform Nucleus |
| **6** | 760 | 27.9 | 5 | 53.6 | 0.014 | 30 | 4 | 54 | 6 | R | Frontal | Sub-Gyral |
| | | | | | 0.009 | 24 | 10 | 60 | 6 | R | Frontal | Sub-Gyral |
| **7** | 696 | −44.6 | 3.4 | 34 | 0.014 | −44 | 2 | 34 | 6 | L | Frontal | Precentral Gyrus |