

# Identification of Common Neural Circuit Disruptions in Cognitive Control Across Psychiatric Disorders

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**Objective:** Cognitive deficits are a common feature of psychiatric disorders. The authors investigated the nature of disruptions in neural circuitry underlying cognitive control capacities across psychiatric disorders through a transdiagnostic neuroimaging meta-analysis.

**Method:** A PubMed search was conducted for whole-brain functional neuroimaging articles published through June 2015 that compared activation in patients with axis I disorders and matched healthy control participants during cognitive control tasks. Tasks that probed performance or conflict monitoring, response inhibition or selection, set shifting, verbal fluency, and recognition or working memory were included. Activation likelihood estimation meta-analyses were conducted on peak voxel coordinates.

**Results:** The 283 experiments submitted to meta-analysis included 5,728 control participants and 5,493 patients with various disorders (schizophrenia, bipolar or unipolar depression, anxiety disorders, and substance use disorders). Transdiagnostically abnormal activation was evident in the

left prefrontal cortex as well as the anterior insula, the right ventrolateral prefrontal cortex, the right intraparietal sulcus, and the midcingulate/presupplementary motor area. Disruption was also observed in a more anterior cluster in the dorsal cingulate cortex, which overlapped with a network of structural perturbation that the authors previously reported in a transdiagnostic meta-analysis of gray matter volume.

**Conclusions:** These findings demonstrate a common pattern of disruption across major psychiatric disorders that parallels the “multiple-demand network” observed in intact cognition. This network interfaces with the anterior-cingulo-insular or “salience network” demonstrated to be transdiagnostically vulnerable to gray matter reduction. Thus, networks intrinsic to adaptive, flexible cognition are vulnerable to broad-spectrum psychopathology. Dysfunction in these networks may reflect an intermediate transdiagnostic phenotype, which could be leveraged to advance therapeutics.

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Cognitive control, or executive functions, refer to those processes that are integral to the effortful deployment of cognitive resources for flexible, adaptive responding to shifting contingencies—and ultimately accommodating to the demands of daily life. Accordingly, cognitive control capacity predicts socio-occupational stability and success as well as broader measures of quality of life (1).

Latent variable analysis of neuropsychological performance has shown that intact cognition consists of interrelated executive functions, including updating (i.e., monitoring working memory store), inhibition (resisting prepotent responses), and shifting (switching between mental sets). An underlying, largely heritable, common factor reflecting general cognitive control capacity also emerges (2, 3). Across various psychiatric disorders, neuropsychological performance is broadly (i.e., domain nonspecifically) perturbed, with some variations in severity (4, 5). Evidence from large-scale phenotypic studies

has also demonstrated a dimension of general psychopathology that cuts across disorder boundaries (6). This dimension robustly accounts for lifespan functional impairment and prospective psychopathology above and beyond current symptom-based predictions (7, 8). Higher loadings on the general psychopathology factor predict worse performance on tasks of working memory and planning as well as limited academic achievement and lower IQ (7). Thus, a general liability for cognitive dyscontrol, which traverses both cognitive domains and diagnostic boundaries, may be a core feature of mental illness.

Evidence for common, largely heritable liabilities to experiencing general psychopathology as well as cognitive dyscontrol prompts the question of whether there are accompanying structural anomalies seated within the neurocircuitry subserving cognitive control. We recently completed a meta-analysis of volumetric differences in axis I patients and matched control groups (9). Across 193 whole-brain voxel-

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based morphometry studies of nearly 16,000 individuals representing diverse diagnostic classes (schizophrenia, bipolar and unipolar depression, anxiety disorders, and substance use disorders), we found that gray matter loss converged across diagnoses in three regions: the dorsal anterior cingulate and the left and right anterior insula. In an independent sample of healthy individuals, we found that lower gray matter volume in these regions predicted worse behavioral performance on measures of higher-level cognitive control but was unrelated to more rudimentary processing speed. These findings suggest a coordinated structural perturbation of a closely interconnected anterior-cingulo-insular or “salience network” across disorders, likely associated with transdiagnostic deficits in executive function tasks.

The insula and anterior cingulate, as part of the broader “salience network” (10), feature prominently in intact (11) as well as disordered emotional responding (12). However, the insula and anterior cingulate are deployed beyond emotional processing, more generally coordinating dynamic neural network interactions in response to contextual demands (13–15). Critical to cognitive control is their coordination with the fronto-parietal network to function as a superordinate or “multiple-demand” cognitive processing network (16–26). That is, in tasks ranging from working memory to inhibiting irrelevant information and selecting competing task-relevant responses (17), the dorsal anterior cingulate and left and right anterior insula extending to the ventrolateral prefrontal cortex are recruited in conjunction with the midcingulate cortex extending into the presupplementary motor area; the left dorsolateral prefrontal cortex extending from the middle frontal gyrus to the inferior frontal junction/gyrus and premotor cortex; and the inferior parietal cortex extending into the intraparietal sulcus. Findings have been mixed in terms of which multiple-demand network nodes show dissociable sensitivity to phasic (i.e., moment-to-moment) versus sustained (i.e., set maintenance) cognitive demands (e.g., 20–22). However, the salience network (often referred to as the cingulo-opercular network in the cognitive task literature) and the fronto-parietal network reliably coordinate as subnetworks of a broader, coherent multiple-demand network. Similar to the latent or common cognitive control factor observed in behavioral measures of cognitive processing, the activity of this network suggests a “common core” recruited across diverse cognitive challenges (18).

Taken together, behavioral and structural evidence implicates transdiagnostic disruptions in the neurocircuitry underlying general cognitive control capacity. In this study, we examined whether there is a parallel transdiagnostic functional impairment in whole brain activation during cognitive control task performance. We hypothesized that deficits would be particularly manifest in the multiple-demand network or the common core of cognitive processing, including in regions we previously observed as transdiagnostically structurally perturbed (9).

## METHOD

### Experiment Inclusion Criteria and Identification

Articles were identified by searching PubMed for functional neuroimaging experiments of cognitive control tasks

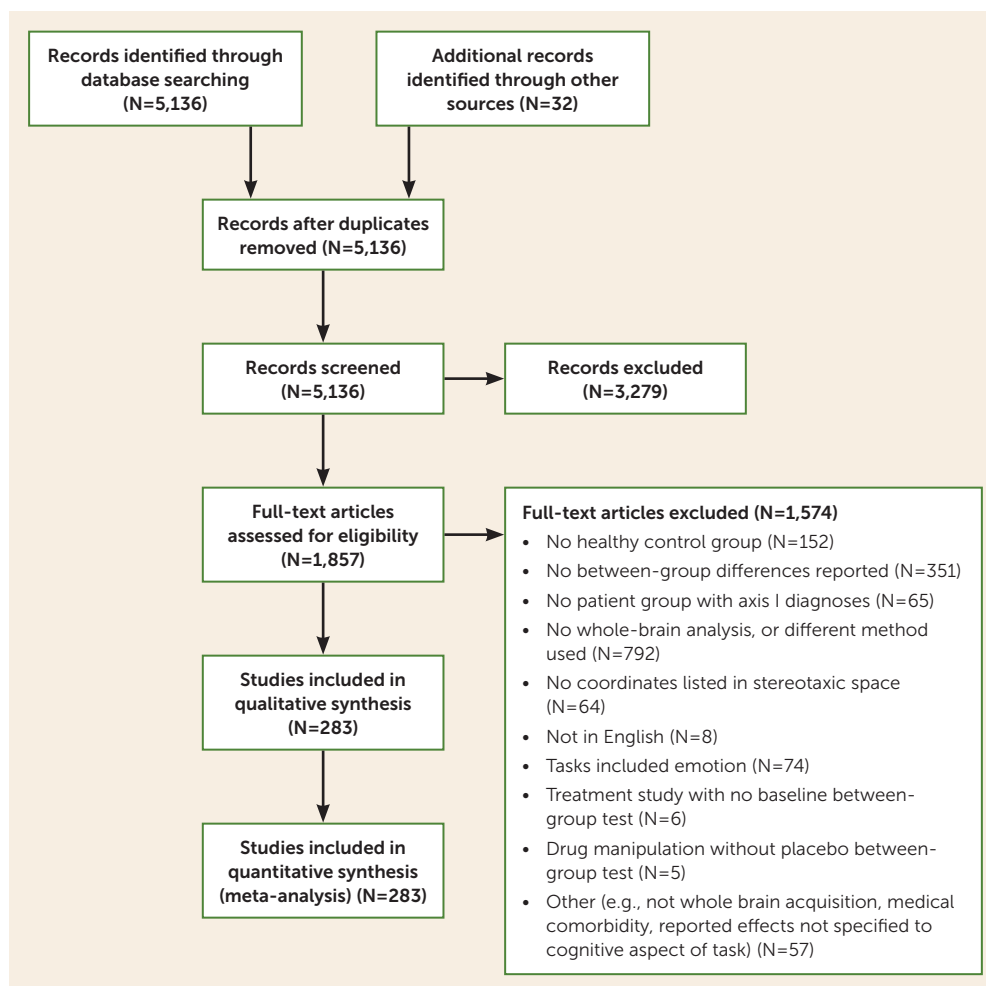
published through June 2015 that compared patients with axis I disorders to matched control participants (Figure 1). Experiments were eligible if they 1) examined cognitive control tasks with functional neuroimaging, 2) performed whole-brain analysis, 3) included a comparison between patients with axis I disorders and matched healthy control participants during cognitive challenges, and 4) reported coordinates in a defined stereotaxic space (e.g., Talairach or Montreal Neurological Institute [MNI] space).

Experimental procedures must have included diagnostic interview of axis I patients and control participants, with patient groups exceeding the clinical threshold for diagnosis. A psychotic disorders category comprised schizophrenia and schizoaffective, schizophreniform, and delusional disorders. A nonpsychotic disorders category comprised bipolar and unipolar (major depression, dysthymia) depressive disorders, anxiety disorders (including obsessive-compulsive and posttraumatic stress disorders), and substance use disorders (mixed substance abuse and/or dependence). Experiments with fully remitted patient samples were excluded.

Individuals with a principal diagnosis of a depressive or a bipolar disorder who also presented with psychotic features were excluded by criteria in the original experiments. Across disorders, patient participants included those with first-episode and chronic disorder manifestations, including interepisode states of bipolar and psychotic disorders. The substance use disorders included chronic users of a range of substances, currently active or abstinent, but not in acute withdrawal. Experiments were selected to capture lifespan patterns and thus included participants ranging in age from childhood through older adulthood. Axis I diagnoses presenting predominantly in childhood (e.g., attention deficit hyperactivity disorder) or those associated with altered developmental trajectories of brain structures inherent to expression of disorder phenotypes (e.g., autism spectrum disorders) were excluded.

Articles with experimental tasks probing a wide range of processes related to cognitive control were included, categorized into eight domains: conflict monitoring, performance monitoring, response inhibition, response selection, set shifting, verbal fluency, recognition memory, and working memory. A ninth category, “other,” included 18 disparate experiments that did not cohere with one of these domains (see Table S1 in the data supplement that accompanies the online edition of this article). To target substrates of higher-order cognitive control, experiments that focused on simple processing speed or orienting in the context of passive perception (e.g., oddball discrimination) were excluded. Cognitive processing experiments with embedded affective manipulations (e.g., affective stimuli, mood induction) were also excluded.

Peak coordinates for whole brain between-group comparisons under cognitive challenge were required. Interactions were included if follow-up tests clarified patterns of patient hyper- versus hypoactivation during cognitive challenge. Experiments reporting results only for small-volume

**FIGURE 1. Flow Diagram of Study Selection in an Analysis of Neural Circuit Disruptions in Cognitive Control Across Psychiatric Disorders**

correction or within a region of interest were excluded. Articles with reported contrasts that did not reflect cognitive demand were excluded. If multiple contrasts were reported in a single paper, only those pertaining to the most challenging condition were included. All coordinates reported in Talairach space were converted into MNI space (27).

#### Activation Likelihood Estimation (ALE) Meta-analysis

The revised ALE algorithm, implemented in MATLAB, was used to identify areas of convergence of reported coordinates for patient/control differences in activation during cognitive control tasks higher than expected under a random spatial association (28, 29, 30; see also the Supplementary Methods section in the online data supplement). The resulting nonparametric *p* values were thresholded at a cluster-level family-wise-error-corrected threshold of  $p < 0.05$  (cluster-forming threshold at voxel-level  $p < 0.005$ ) and transformed into *z* scores for display. To avoid results dominated by one or two individual experiments and to have sufficient power to detect moderately sized effects, ALE analyses were limited to those contrasts with at least 20 experiments (31).

We conducted the following analyses:

1. Pooling across coordinates of hypo- and hyperactivation in patients relative to controls to identify trans-diagnostic patterns of “aberrant activation.”
2. A conjunction between these results and the multiple-demand network from three large meta-analyses in healthy participants (25, retrieved through ANIMA [32], <http://anima.fz-juelich.de>).
3. A conjunction with the nodes of common gray matter decrease revealed by Goodkind et al. (9).
4. Separate ALE analyses on hyper- or hypoactivation coordinates (i.e., patient > control or control > patient).
5. Guided by our previous work (9) and phenotypic structural models (33), we distinguished between psychotic and nonpsychotic disorders. Given sufficient numbers of experiments (31), we performed ALE by broad diagnostic groupings (i.e., schizophrenia, bipolar and unipolar depression, anxiety disorders, and substance use disorders).

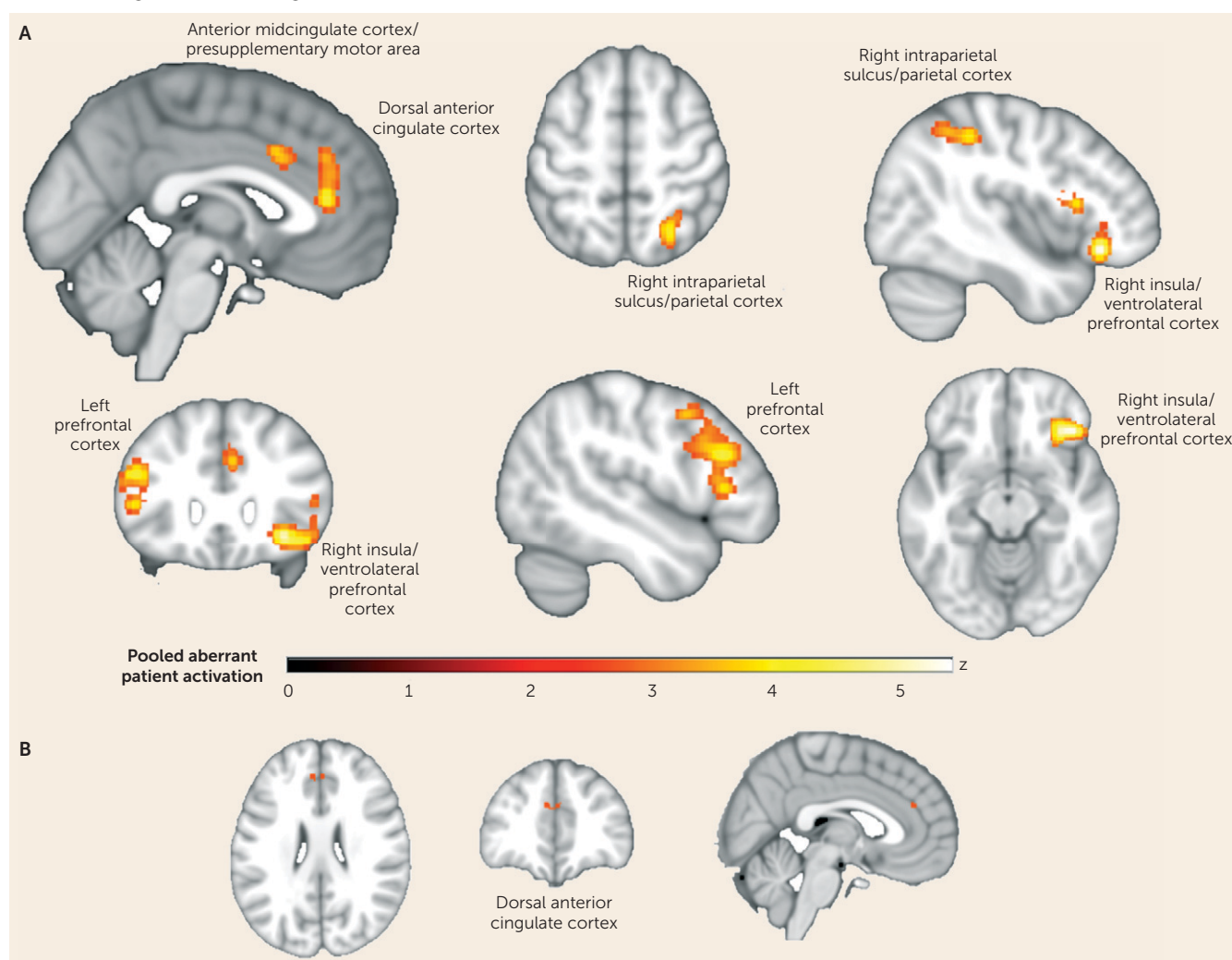
6. Follow-up analyses on extracted data (probability of voxelwise activation from the modeled activation maps) in significant clusters to examine the contribution of demographic, disorder, medication, and task-related factors.

Nonparametric Wilcoxon signed rank tests, Kruskal-Wallis tests, and Mann-Whitney *U* tests were utilized as warranted.

## RESULTS

#### Final Selected Experiment Set

The final set of experiments consisted of 283 experiments from 251 articles (Figure 1; see also Tables S1 and S2 in the online data supplement) covering 11,221 participants (5,493 patient and 5,728 control participants). (For more details on the included experiments, see the supplementary material.) The vast majority of experiments (N=260) used functional MRI; the remainder included 21 positron emission

**FIGURE 2. Regions of Transdiagnostic Aberrant Activation<sup>a</sup>**

<sup>a</sup> Panel A shows regions of transdiagnostic aberrant activation (i.e., pooled across patient hyper- and hypoactivation) (red/yellow). In panel B, a conjunction with the regions of gray matter loss observed by Goodkind et al. (9) highlights anatomical and functional correspondence in the dorsal anterior cingulate (orange).

tomography experiments and one each using arterial spin labeling and single-photon emission computerized tomography. Mean ages ranged from 11.2 to 73.3 years. Psychotic (N=139) and nonpsychotic disorders (N=144) were represented nearly equally. The included experiments also represented an array of cognitive tasks across multiple domains: working memory (N=100), response inhibition (N=42), recognition memory (N=37), conflict monitoring (N=31), verbal fluency (N=17), set shifting (N=15), response selection (N=12), performance monitoring (N=11), and a set of 18 diverse experiments outside of these domains. Most experiments included medicated (N=193) as opposed to unmedicated patients (N=60); information on medication was lacking for 30 experiments.

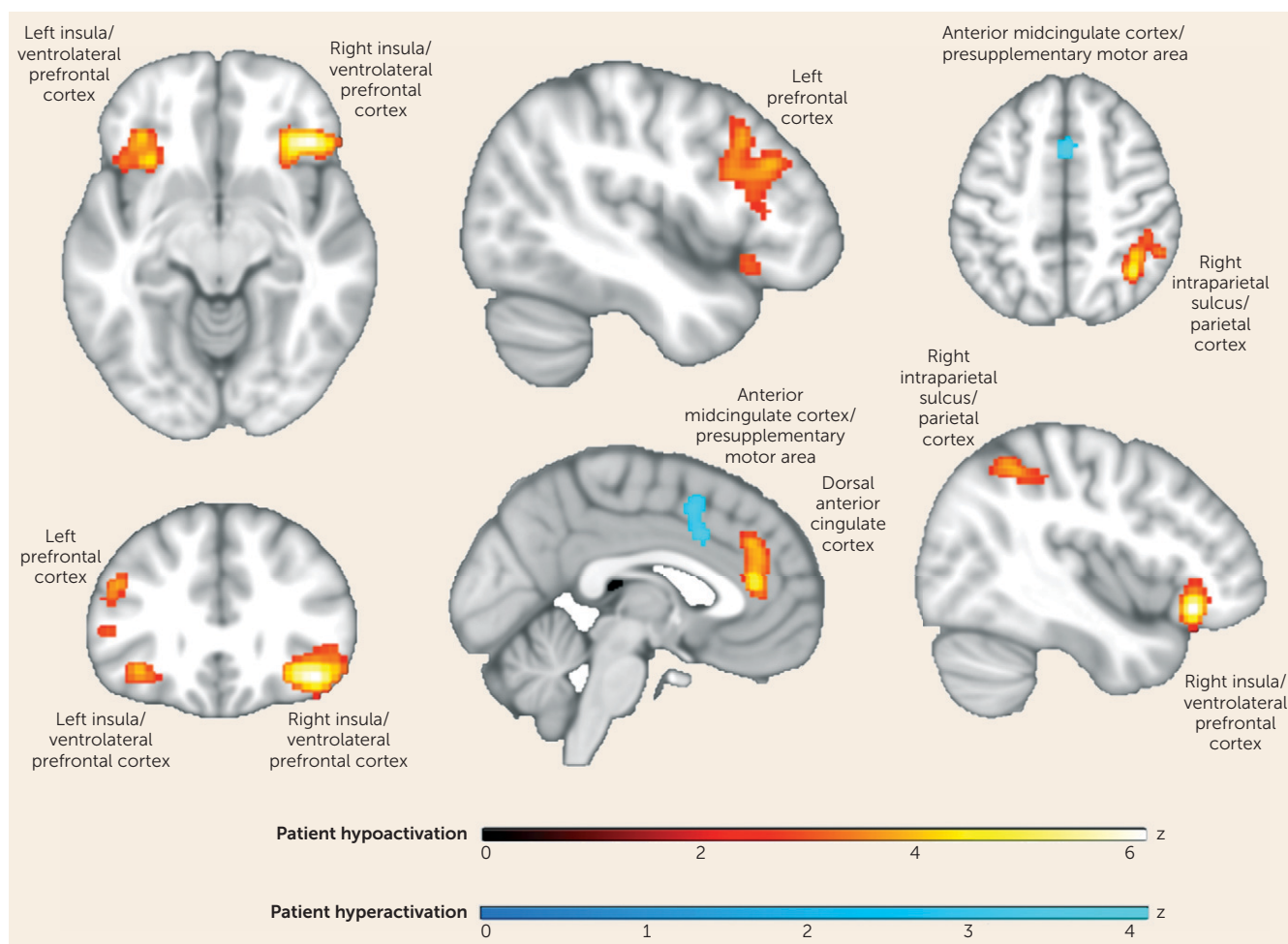
### Meta-Analysis Results Across Disorders

*Activation patterns during cognitive control: voxelwise analyses.*

*Transdiagnostic aberrant activation:* Pooling across patterns of patient hyper- and hypoactivation to assess “aberrant

activation” at the whole brain level revealed patient abnormalities in the dorsal anterior cingulate, the anterior midcingulate cortex/presupplementary motor area, the right insula (extending to the ventrolateral prefrontal cortex), and the right intraparietal sulcus, as well as a cluster in the left prefrontal cortex extending from the middorsolateral prefrontal to the premotor cortex (Figure 2A; see also Table S3 in the online data supplement). This pattern suggests disruption of a network of regions similar to the multiple-demand network (25) that may overlap with nodes of transdiagnostic gray matter loss. Furthermore, a broad distribution of disorders and domains contributed to each cluster of convergence (see Table S4 in the data supplement).

A conjunction with the multiple-demand network identified from meta-analyses of healthy participants (25) highlights overlap in the left inferior frontal gyrus/junction, the presupplementary motor area, the right anterior insula/ventrolateral prefrontal cortex, and the right intraparietal

**FIGURE 3. Transdiagnostic Patterns of Hyper- and Hypoactivation in Patients<sup>a</sup>**

<sup>a</sup> Within the anterior cingulate, hypoactivation (orange) was seen in an anterior dorsal cingulate region that overlaps with a region prone to gray matter loss in our previous work (9). An anterior midcingulate/presupplementary motor area cluster that overlaps with the multiple-demand network showed patient hyperactivation (blue). All other regions of the cognitive control circuit showed consistent patient hypoactivation (orange).

sulcus (see Figure S1 and Table S5 in the data supplement). A conjunction with the regions of transdiagnostic gray matter loss observed by Goodkind et al. (9) shows similar cross-modality disruptions in regions of the dorsal anterior cingulate and right insula, with exact correspondence in the dorsal anterior cingulate (Figure 2B; see also Figure S2 in the data supplement). This suggests two distinct posterior-medial frontal effects, one being disruption within a node of the multiple-demand network and one in a more anterior node shown to be especially vulnerable to gray matter loss.

**Transdiagnostic hyper- versus hypoactivation:** The distinction between anterior and midcingulate effects was further underscored when we tested separately for convergent hyper- versus hypoactivation in patients. The more anterior dorsal cingulate overlapping with regions prone to gray matter loss showed patient hypoactivation, whereas the anterior midcingulate/presupplementary motor cortex overlapping with the canonical multiple-demand network showed patient hyperactivation (Figure 3; see also Table S6 in

the data supplement). All other regions of the cognitive control circuit showed patient hypoactivation. Bilateral hypoactivation of the insula, extending to the ventrolateral prefrontal cortex, was also evident. These patterns persisted when ALE was rerun systematically excluding the experiments using arterial spin labeling and single-photon emission computerized tomography (see Figure S3 and Table S7 in the data supplement), the tasks that did not cohere in a domain (see Figure S4 and Table S8), and the experiments with children and older adults (see Figure S5 and Table S9).

Next we examined whether factors of age, medication, and behavioral performance might affect these patterns. The majority of experiments represented adulthood (N=248; ages 18–50 years), followed by childhood/adolescence (N=27; age <18 years), and there were few studies of older adulthood (N=8; age >50 years). Since excluding children and older adults had little impact on activation patterns but results from these groups contributed to convergence (see Table S10 in the data supplement), we computed the aberrant activation contrast stratified by age group. No clusters converged in the



older adult sample, although this sample included too few studies for valid ALE inference (31). By contrast, the child/adolescent sample showed strong right anterior insula/ventrolateral prefrontal cortex activation overlapping with the adult sample (see Figure S6 and Table S11 in the data supplement), suggesting a particular role of this node in cognitive dyscontrol from childhood through adulthood.

Next we considered current psychotropic medication status, as 68% of the experiments included medicated patients. Medication did not influence patterns of hypoactivation in multiple-demand network nodes (see Figure S7 and Table S12 in the data supplement). Medicated patients, however, showed hyperactivation specific to the anterior midcingulate cortex/presupplementary motor cortex, also evident in contribution analyses (see Table S10 in the data supplement). Experiments with unmedicated patients did not show any (whole brain significant) hyperactivations. Moreover, accounting for behavioral performance on the scanner task demonstrated that patient hyperactivation in the anterior midcingulate/presupplementary motor cortex cluster was primarily driven by patient groups that performed on par with, as opposed to worse than, control participants (see Figure S8 and Tables S10 and S13 in the data supplement). By contrast, patient hypoactivation in multiple-demand network nodes was largely similar regardless of whether behavioral performance was impaired.

*Accounting for psychotic and nonpsychotic disorders:* Examining psychotic and nonpsychotic disorders separately revealed aberrant activation in psychotic disorders in the anterior midcingulate/presupplementary motor cortex and the left prefrontal cortex extending posteriorly from the middorsolateral prefrontal to the premotor cortex. Nonpsychotic disorders showed aberrant activation in the right anterior insula/ventrolateral prefrontal cortex and the right intraparietal sulcus (Figure 4A; see also Tables S14 and S15 in the data supplement). A contrast revealed that aberrant activation in a posterior portion of the left prefrontal cluster as well as a medial portion of the midcingulate/presupplementary motor area was more characteristic of psychotic disorders (see Figure S9 and Tables S14 and S15 in the data supplement), whereas aberrant activation in the right intraparietal sulcus and a more anterior portion of the right anterior insula/ventrolateral prefrontal cortex cluster was more specific to nonpsychotic disorders.

No hyperactivation regions survived whole brain correction for either psychotic or nonpsychotic disorders. Hypoactivation specific to psychotic disorders emerged, again, in the left lateral prefrontal cluster (Figure 4B; see also Tables S16 and S17 in the data supplement). Hypoactivation for both disorder classes emerged in the right anterior insula/ventrolateral prefrontal cortex, confirmed with a conjunction analysis to correspond to the multiple-demand network. Contrasting hypoactivation in psychotic and nonpsychotic disorders further highlighted the fact that the right anterior insula/ventrolateral prefrontal cortex extended more anteriorly in nonpsychotic disorders, whereas psychotic

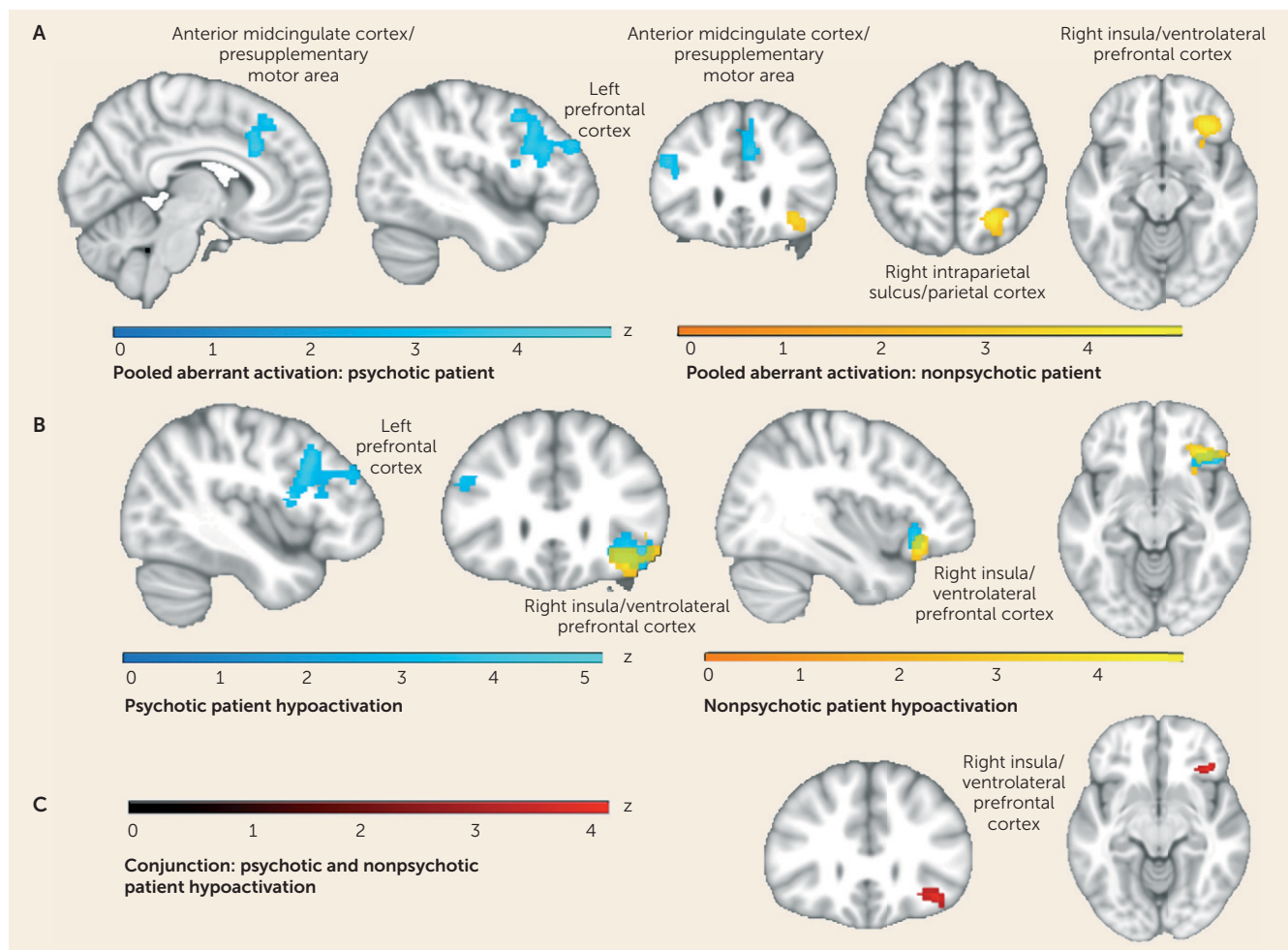
disorders showed stronger hypoactivation in the posterior portion of the left prefrontal cluster (see Figure S10 in the data supplement).

*Accounting for disorders and task domains:* Patients with schizophrenia spectrum disorders showed a reliable hypoactivation of the left prefrontal cortex as well as right ventrolateral prefrontal cortex clusters consistent with the overall pattern. Patients with substance use disorders showed hyperactivation in the right posterior parietal cortex (more posterior than the overall pattern) (see Figure S11 and Table S18 in the data supplement). Finally, although our focus was on “multiple-demand” or “general cognitive” processing, we also assessed the contribution of different domains to the overall convergence. Domain-specific ALE (as well as domain-by-disorder analyses) was performed for contrasts with at least 20 experiments (31), and these are reported in the online data supplement (see Figures S12 and S13 and Tables S19 and S20). In summary, while transdiagnostic results demonstrate the wide distribution of individual disorders and domains to the ALE maps, refining ALE to specific diagnoses and domains revealed few activations that survived whole brain correction, likely because of power limitations.

*Region-of-interest analyses.* Per-voxel probabilities in regions of significant convergence from the multiple-demand and salience networks were extracted from the transdiagnostic hyper- and hypoactivation data and examined for effects of age groups, psychotic versus nonpsychotic disorders, individual disorder classes, medication status, and behavioral performance. Psychotic relative to nonpsychotic disorders showed stronger hypoactivation in the left prefrontal cortex (Mann-Whitney U test,  $U=10,994.5$ ,  $p<0.05$ ). Specifically, schizophrenia showed substantially more hypoactivation than each of the nonpsychotic disorders (except substance use disorders), which in turn did not differ from each other (Figure 5). Regarding the transdiagnostic patient hyperactivation in the anterior midcingulate/presupplementary motor cortex, patient samples whose behavioral performance was on par with that of control participants (mean per-voxel probability=1.0) were more likely to show hyperactivation than patient samples that performed worse (mean per-voxel probability=0.29) ( $U=9,270$ ,  $p<0.05$ ). No other group differences were observed in the extracted data.

## DISCUSSION

In a meta-analysis of cognitive control tasks across axis I disorders, we observed a transdiagnostic pattern of aberrant brain activation in regions corresponding to the well-established multiple-demand network (16–26), including the left prefrontal cortex (from premotor to middorsolateral prefrontal cortex), the right insula extending to the ventrolateral prefrontal cortex, the right intraparietal sulcus, and the anterior midcingulate/presupplementary motor cortex. Abnormal activation was also observed in a separate, more

**FIGURE 4. Patterns of Brain Activation in Psychotic and Nonpsychotic Disorders<sup>a</sup>**

<sup>a</sup> As shown in panel A, aberrant activation (pooling across hyper- and hypoactivation) emerged for patients with psychotic disorders (blue) in the anterior midcingulate/presupplementary motor area and the left prefrontal cortex extending posteriorly from the middorsolateral prefrontal cortex to the inferior frontal gyrus/junction and premotor cortex. Nonpsychotic disorders showed aberrant activation (yellow) in the right anterior insula/ventrolateral prefrontal cortex and the right intraparietal sulcus. In separate analyses of psychotic and nonpsychotic disorders (panel B), hypoactivation in the left middorsolateral prefrontal cortex to the inferior frontal gyrus/junction and premotor cortex characterized psychotic disorders (blue). Hypoactivation for both disorder classes emerged in the right anterior insula/ventrolateral prefrontal cortex (nonpsychotic disorders=yellow). Hyperactivation contrasts did not show any significant whole-brain activations. A conjunction of hypoactivation across psychotic and nonpsychotic disorders (panel C) revealed shared dysfunction in the right anterior insula/ventrolateral prefrontal cortex (red).

anterior dorsal anterior cingulate cluster (as well as the insula), suggestive of concurrent disruption in regions we previously observed (9) as transdiagnostically prone to reduced gray matter.

Unlike patient hypoactivation, patient hyperactivation was isolated to the anterior midcingulate/presupplementary motor cortex. Consistent with a role in the implementation and maintenance of task sets (34) as well as the translation to overt action (35), patient hyperactivation in the anterior midcingulate/presupplementary motor cortex was primarily driven by experiments for which predominantly medicated patients performed on par with control participants, as opposed to those for which patients performed worse. Increased anterior midcingulate/presupplementary motor cortex activation in patients relative to control participants may reflect a compensatory process for maintaining intact

performance amid deficiencies in other network nodes (i.e., proactive/reactive control [36]).

Given that the swath of cortex extending from the anterior to the midcingulate/presupplementary motor cortex has been characterized as part of a coherent salience network (10, 15), the discordant hypo- and hyperactivation observed here between the more anterior and posterior cingulate, respectively, might seem unexpected. However, parcellation of the intrinsic functional connectivity of the anterior insula has revealed subnetworks that differentiate these regions. While both the ventral and dorsal anterior insula support cognitive processing (36), the dorsal portion is more closely coupled with the anterior midcingulate/presupplementary motor cortex (marked here by patient hyperactivation) and appears to promote cognitive flexibility (37). The ventral anterior insula (marked here by patient hypoactivation) is more

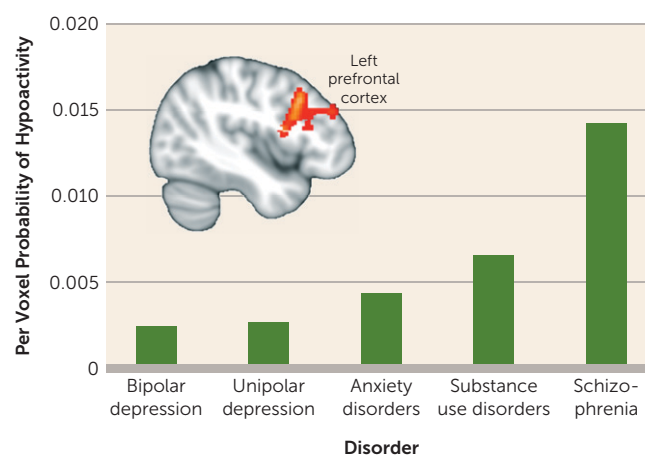
closely coupled with the anterior dorsal cingulate (marked here by corresponding hypoactivation) and relates more to motivational engagement (36). Whole brain graph theoretical approaches have similarly revealed this distinction, leading to speculation that the more anterior cingulate subnetwork is more characteristic of the salience network, whereas the more posterior cingulate subnetwork is more representative of a cingulo-opercular task control network (38).

Differences in the extent of disruption also emerged between psychotic and nonpsychotic disorders. Psychotic disorders, particularly schizophrenia, showed pronounced hypoactivation of the left lateral prefrontal cluster, particularly the more posterior portion. Meta-analytic coactivation-based parcellation of this region has suggested that while the left prefrontal cortex is broadly recruited for adaptive cognitive control, the predominant processes are typically more top-down, moving anteriorly from the premotor to the middorsolateral prefrontal cortex (39, 40). The consistent hypoactivation across this cortical gradient, including the more posterior portion subserving more rudimentary processes, may reflect the broad and more severe cross-domain disruption of neuropsychological performance in schizophrenia relative to other disorders (4). In contrast, particularly convergent hypoactivation across disorders emerged in the right anterior insula/ventrolateral prefrontal cortex. This network switchboard or hub appears especially vulnerable to both gray matter loss and functional impairment across psychopathology.

Concurrent disruptions in the salience and multiple-demand networks highlight a means by which transdiagnostic gray matter reduction in the dorsal anterior cingulate and insula might influence cognitive control capacity and, furthermore, how affective and neurocognitive deficits in psychopathology may so often be expressed simultaneously. That is, these highly coordinated regions are sensitive to demands on either cognitive control or emotional processing (17).

Our findings are also consistent with the broader role of the anterior cingulate and insular cortices as coordinating network interactions in the service of goal-directed behavior (41, 42). For example, recent work on causal interactions among nodes of multiple-demand and salience networks (43, 44) suggests that the anterior insula amplifies salience detection in the anterior and midcingulate cortices in a manner proportional to both cognitive demand and individual capacity. This in turn prompts activation of the fronto-parietal subnetwork, particularly lateral prefrontal regions and the parietal cortex. Furthermore, a coactivation-based parcellation of the lateral prefrontal cortex across cognitive paradigms (45) revealed two functional subregions, with the anterior region preferentially connected to the anterior cingulate and the posterior region to the intraparietal sulci. In short, accumulating evidence supports strong functional integration among the salience and multiple-demand networks and subnetworks during intact cognitive processing, and the present findings suggest that their coordination is vulnerable to disruption across disorders.

**FIGURE 5. Probability of Hypoactivation of the Left Prefrontal Cortex, by Disorder Class<sup>a</sup>**



<sup>a</sup> In a voxelwise analysis, patients with psychotic disorders showed a prominent hypoactivation in the left prefrontal cortex (inset). The extracted per-voxel probability of control > patient activation in this region of interest revealed that schizophrenia was more likely to show hypoactivation than each of the nonpsychotic disorders (except substance use disorders), which in turn did not differ from each other.

Our study has several limitations. First, the number of included experiments varied substantially among the cognitive domains, as it did among the disorders. We observed strong evidence of a domain general cognitive control disruption in fronto-parietal-cingular-insular networks, with limited diagnosis-specific effects. The latter may reflect the typically less severe neuropsychological impairments of disorders other than schizophrenia (4), or simply a lack of power due to the limited corpus of published papers for some disorders, or the fact that ALE probes spatial convergence without accounting for individual effect sizes. Additionally, polythetic diagnostic schemes, comorbidity, and the inherent difficulty of establishing consensus on principal disorder could hamper detection of cognitive control impairment profiles of putatively “pure” disorder manifestations and instead contribute to common patterns. Likely influential factors, such as medication types, illness duration, and comorbidity, could not be comprehensively assessed because of incomplete reporting across studies. Furthermore, given the paucity of published study sets in children and older adults, our findings are most applicable to (younger) adults. Lastly, while this is the most comprehensive meta-analysis of functional neuroimaging of cognitive processing in axis I disorders, the included studies do not represent the whole of the extant literature, including the vast number of studies focused on specific regions of interest.

## CONCLUSIONS

Neuropsychological performance, gray matter volume, and now functional brain activation evidence converge to implicate transdiagnostic disruptions in the neurocircuits underlying general cognitive control capacity. Functional



disruptions parallel the multiple-demand network and its interface with the salience network. Essentially, networks intrinsic to adaptive, flexible cognition are vulnerable to a broad spectrum of psychopathology. These findings highlight a common intermediate phenotype (46–48), which could be leveraged to advance therapeutics. Multimodal interventions that target the foundation of intact, dynamic cognition seated in these frontal-parietal-cingular-insular networks could be powerful for ameliorating not only symptomatic distress but also the often pervasive functional impairments and diminished quality of life prevalent across psychiatric disorders.

## AUTHOR AND ARTICLE INFORMATION

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