



Review article

Transdiagnostic impairment of cognitive control in mental illness

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ABSTRACT

Intact cognitive control or executive function has characteristic patterns in both behavior and functional neurocircuitry. Functional neuroimaging studies have shown that a frontal-cingulate-parietal-insular (i.e., “multiple demand”) network forms a common functional substrate undergirding successful adaptation to diverse cognitive processing demands. Separate work on intact neurocognitive performance implicates a higher order factor that largely explains performance across domains and may reflect trait cognitive control capacity. In the current review we highlight findings from respective psychiatric disorders (i.e., psychotic, bipolar and unipolar depressive, anxiety, and substance use disorders) suggesting that cognitive control perturbations amidst psychopathology are most pronounced within these common brain and behavioral indices of adaptive cognitive functioning and moreover, are evident across disorders (i.e., transdiagnostically). Specifically, within each of the disorder classes impairments are consistent in the multiple demand network across a wide range of cognitive tasks. While severity varies between disorders, broad as opposed to domain-specific impairments consistently emerge in neurocognitive performance. Accumulating findings have revealed that phenotypically diverse psychiatric disorders share a common factor or vulnerability to dysfunction that is in turn related to broad neurocognitive deficits. Furthermore, we have observed that regions of the multiple demand network, which overlap with the salience network (dorsal anterior cingulate and bilateral anterior insula) are characterized by reduced gray matter transdiagnostically and predict weaker neurocognitive performance. In summary, transdiagnostic (as opposed to disorder-specific) patterns of symptomatic distress and neurocognitive performance deficits, concurrent with parallel anomalies of brain structure and function may largely contribute to the real-world socio-occupational impairment common across disorders.

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Cognitive control or executive functions refer to those processes integral to the effortful deployment of cognitive resources for flexible, adaptive responding to shifting contingencies. As such, cognitive control undergirds the self-regulation imperative for successful, dynamic accommodation to the demands of daily life (cf. [Diamond, 2013](#) for review). Even among healthy individuals, cognitive control capacity predicts endeavors and success in educational performance and attainment ([Duncan et al., 2007](#)), occupational stability and advancement ([Foxall, 2014](#)), health promotion ([McClernon et al., 2015](#); [Riggs et al., 2010](#)), as well as broader measures of overall quality of life ([Davis et al., 2010](#)). Given the influence on functional status among healthy individuals, cognitive control/executive functions are likely integral to the development, resistance to, maintenance, and remediation of psychopathology. That is, as phasic (or prolonged) distress manifests in the context of mental health or illness, cognitive control neurocircuits are likely recruited in the service of symptom regulation. In fact, meta-analysis of functional neuroimaging studies of adaptive emotion regulation demonstrate the recruitment of neural networks characteristic of cognitive control—a frontoparietal network containing the dorsolateral prefrontal and posterior parietal cortices, and a cingulo-opercular network containing the dorsal anterior cingulate cortex (dACC), anterior insula, and the anterior prefrontal cortex ([Kohn et al., 2014](#)).

The foundation of intact cognitive control has characteristic patterns in both behavior and functional neurocircuitry. As such, cognitive control perturbations amidst psychopathology are potentially most pronounced within indices of these processes common to adaptive functioning and moreover, evident across disorders (i.e., transdiagnostically). In this review we first discuss behavioral evidence of cognitive dyscontrol transdiagnostically, focusing on psychotic, bipolar and unipolar depressive, anxiety, and substance use disorders. Second, to contextualize behavioral correlates of cognitive control anomalies in mental illness relative to underlying structure, we discuss our recent findings from a meta-analysis ([Goodkind et al., 2015](#)) demonstrating transdiagnostic gray matter reductions in a dorsal anterior cingulate-anterior insula-based network. We also highlight the demonstrated functional relevance of this network in terms of impaired cognitive control performance. Next, we focus on the neurocircuitry implicated across psychotic, bipolar and unipolar depressive, anxiety, and substance use disorders in functional neuroimaging studies of cognitive dyscontrol. Finally, we briefly discuss the implications for future research and the potential to leverage cognitive control and its neurocircuitry for innovating powerful and broadly applicable transdiagnostic interventions to ameliorate distress and improve daily real-world functioning.

1. Clues to core cognitive control dysfunction common across psychiatric disorders

1.1. A common underlying cognitive control factor: behavior

Latent variable analysis of performance on a wide array of neuropsychological tasks has shown that intact cognition has a characteristic pattern of interrelated executive functions throughout the lifespan from childhood ([Lehto et al., 2003](#)) through middle ([Miyake et al., 2000](#)) and older adulthood ([Adrover-Roig et al., 2012](#)). For example, [Miyake and colleagues \(2000, 2012\)](#) have demonstrated that updating (i.e., monitoring and refreshing working memory store), inhibition (resisting prepotent responses), and shifting (switching between mental sets) largely explain cognitive processes. Alternatively, [Alvarez and Emory \(2006\)](#) have highlighted the synergy of working memory, inhibition, and

selective attention. The fact that diverse functions show coherence suggests that these heterogeneous processes may work in tandem to promote cognitive wellbeing, but may also share a vulnerability to dysfunction.

In fact, latent variable analysis of task batteries spanning multiple domains of cognitive control suggest that hallmark executive functions are explained not only as subprocesses such as updating, inhibition, and shifting, but also an underlying common factor reflecting general cognitive control capacity ([Miyake and Friedman, 2012](#)). The extent of impairment in this common factor has yet to be examined in most psychiatric disorders. Historically, hallmark symptoms of individual disorders have prompted hypotheses about domain-specific impairments in neuropsychological profiles per disorder (e.g., poor resistance to interference in PTSD due to intrusions). As such, investigations on respective disorders have typically focused on one or two exemplar tasks of a given domain, precluding latent variable analysis to discern contributions of a common cognitive control factor. However, taken together the extant literature on neuropsychological performance shows broad (i.e., domain non-specific) rather than distinct performance impairments in studies of individual psychiatric disorders.

Evidence of broad impairments for respective disorders and classes of related disorders, albeit with variations in severity, was clearly demonstrated by [Snyder et al. \(2015\)](#). The authors summarized the effect sizes of meta-analyses of cognitive control/executive functions by individual disorder. For consistency with prevailing latent variable models, results for individual tasks were aggregated into domains of shifting, inhibition, updating, and working memory manipulation and maintenance. Measures of planning and verbal fluency, which typically recruit multiple executive functions and thus do not clearly load one of the other factors, were also summarized across studies as they have been examined frequently in clinical samples. Schizophrenia showed the most pronounced and consistently cross-domain deficits, aligned with the severe functional impairment characteristic of the disorder ([Harvey and Strassnig, 2012](#)). Specifically, aggregating across eight meta-analyses, schizophrenia demonstrated impairments with large effect sizes on all measures except the relatively less demanding process of working memory maintenance, for which a medium effect sized impairment emerged. Slightly less severe, but nonetheless consistent cross-domain deficits were observed in the average of ten meta-analyses of bipolar disorder. Notably, eight of the ten meta-analyses examined euthymic bipolar disorder, suggesting that cognitive control deficits are present regardless of mood state but are likely more pronounced during acute depression or mania. Unipolar depression showed the same pattern but marked by medium effect sized deficits across all domains with the exception of a lesser impairment on working memory maintenance, a pattern that was similar to, but less severe than in schizophrenia. Aggregating across three meta-analyses of obsessive-compulsive disorder (OCD) and one of posttraumatic stress disorder (PTSD) showed medium to small effect sizes across all domains. Neurocognitive functioning in other (DSM-IV-defined) anxiety disorders (i.e., specific phobia, social anxiety, generalized anxiety, and panic disorders) have been the subject of few published investigations, possibly reflecting the file drawer problem (i.e., hurdles to publishing null results) or a presumption on the part of investigators that cognitive control is uninterrupted in these presentations and thus not examined. Finally, multiple substance use disorders demonstrated deficits foremost in inhibition, but also shifting and working memory. Notably, [Stavro et al. \(2013\)](#) revealed that deficits were typically moderate up to one year of abstinence, and lessened for samples abstinent for at least one year. Despite the paucity of work directly comparing different disorders, taken together these findings have prompted a growing appreciation of

the likelihood of shared deficits in cognitive control capacity across a wide range of Axis I disorders (e.g., Cáceda et al., 2014; Cole et al., 2014; Etkin et al., 2013; Goschke, 2014; Snyder et al., 2015).

1.2. A common underlying psychopathology factor: symptoms

A general liability for cognitive dyscontrol, which cuts across diagnostic boundaries may be related to transdiagnostic vulnerability to mental illness. The historic neo-Kraepelinian approach of the Diagnostic and Statistical Manual of Mental Disorders (e.g., DSM-III, APA, 1980; DSM-5, APA, 2013) and the corresponding International Classification of Diseases of the World Health Organization (ICD-9, WHO, 1977 ICD-10, WHO, 2007) conceptualizes disorders as discontinuous entities with presumably distinct etiologies and biomarkers. However, burgeoning evidence from large-scale phenotypic studies has robustly demonstrated common liabilities across disorders (e.g., Krueger, 1999). For example, examination of disorder patterns in epidemiological samples has revealed a latent internalizing dimension, typically expressed as anxiety or unipolar depressive disorders. A latent externalizing dimension is manifest in substance use and conduct disorders while psychotic disorders load on a third independent thought disorder/psychosis dimension (Kotov et al., 2011; Markon, 2010; Wright et al., 2013). Bipolar disorders and symptoms, likely owing to the relative prominence of psychotic, depressive, and mania features in different samples have at times loaded on the internalizing dimension (Wright et al., 2013) and at others on the psychosis dimension (Kotov et al., 2011). Importantly, recent extensions of this work have shown that these dimensions are, in turn, strongly related to an underlying general psychopathology dimension (Carragher et al., 2016; Lahey et al., 2012). Adult twin studies have revealed a likely genetic basis to these higher- and lower-order dimensions (Kendler et al., 2003, 2011). Furthermore, child and adolescent models have suggested general psychopathology is largely a function of genetic vulnerability, whereas disorder-specific features are more so a function of non-shared environmental influences (Rhee et al., 2015). Notably, the general psychopathology factor robustly accounts for lifespan functional impairment, family history of mental illness, and prospective psychopathology (Caspi et al., 2014; Kim and Eaton, 2015) above and beyond current symptom-based predictions. It is also a more robust predictor of disorder nonspecific factors such as childhood maltreatment, which likely catalyze disorder expression.

Of particular relevance to a potential transdiagnostic liability to cognitive dyscontrol, early childhood and adult neurocognitive functioning is far more strongly related to the underlying general psychopathology factor than the internalizing, externalizing, or thought disorder dimensions (Caspi et al., 2014). More specifically, higher loadings on the general psychopathology factor predict worse performance on neuropsychological tasks of recall, recognition, and working memory, sustained attention and vigilance, and motor planning. General psychopathology also predicts limited early academic achievement as well as lifespan IQ. Finally, at the extreme of this general psychopathology factor, neurocognitive impairments are concurrent with microvascular brain abnormalities, neurological soft signs, receptive language impairment, and IQ deficits (Caspi et al., 2014).

Common cognitive control liability appears distinct from rather than subsumed by the transdiagnostic vulnerability to psychopathology. That is, cognitive control deficits are not clearly a proxy for, cause, or consequence of psychopathology. For example, neurocognitive functioning has meaningfully predicted longitudinal socio-occupational functional outcomes across disorders above and beyond symptom-based predictions (Gyurak et al., 2015; Miller et al., 2015; Tabarés-Seisdedos et al., 2008). In cases of severely

impairing symptomatology in acute episodes of late onset schizophrenia, neurocognitive function is preserved in relation to early onset schizophrenia (Rajji et al., 2009). Further, impairments are evident even prior to the prodromal phase of psychosis (Bora and Murray, 2014). Relatedly, poor cognitive control is not only a consequence of substance abuse, but also an antecedent (e.g., Boelema et al., 2016; Peeters et al., 2014). In the case of major depression, symptom remission following antidepressant treatment has shown no accompanying improvement in neurocognitive deficits spanning multiple domains (Shilyansky et al., in press). Rather than relating to symptom severity or prior antidepressant trial failures, neurocognitive deficits were more pronounced the more chronic the depression. Furthermore, neurocognitive deficits are more pronounced in unaffected relatives of probands than the general population, foremost for schizophrenia (Sitskoorn et al., 2004; Snitz et al., 2006) but also bipolar disorder (Bora et al., 2009; Ivleva et al., 2012; Kim et al., 2015) and substance use disorder (Cservenka, 2016; Gierski et al., 2013). In essence, acute symptom expression does not correspond clearly to manifested neurocognitive deficits. Instead, cognitive control deficits may be a risk factor, intermediate phenotype, or endophenotype of latent psychopathology vulnerability (e.g., Buckholz and Meyer-Lindenberg, 2012; Kozak and Cuthbert, in press; Nolen-Hoeksema and Watkins, 2011). Towards this end, individual differences in general cognitive control capability are almost completely (i.e., 99%) heritable, rendering this factor among the most heritable of psychological traits, exceeding even IQ (Friedman et al., 2008).

1.3. A common underlying structure: gray matter volume

The preponderance of 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. To explore the possibility of such a common substrate, we recently completed a meta-analysis of volumetric differences across Axis I patient and matched control groups (Goodkind et al., 2015). Structural neuroimaging meta-analyses have been reported for a number of psychiatric disorders (e.g., Hamilton et al., 2012; Rotge et al., 2010; Selvaraj et al., 2012). However, these have either focused on single disorders or compared two phenotypically related disorders such as unipolar and bipolar depressive disorders (e.g., Kempton et al., 2011), with an eye towards differences rather than similarities across diagnoses. As such, interpretation of findings has often reflected disorder-specific neural circuit models. Likewise other meta-analyses have not provided spatially unbiased information across the brain (e.g. manual volumetric tracing studies). In meta-analytically summarizing a more complete spectrum of psychopathology across the entire brain, we hypothesized that transdiagnostic commonalities might emerge.

In brief, studies were selected if they (1) used voxel-based morphometry (VBM) to analyze gray matter in patients with a psychiatric diagnosis, (2) included a comparison between these patients and matched healthy control participants, (3) performed a whole-brain analysis, and (4) reported coordinates in a defined stereotaxic space (e.g., Talairach space or Montreal Neurological Institute space). A psychotic disorders category comprised studies of schizophrenia, schizoaffective, schizophreniform, and delusional disorders. A non-psychotic disorders category comprised studies of bipolar depressive disorders, unipolar depressive disorders (major depression, dysthymia), anxiety disorders, and substance use disorders (mixed substance abuse and/or dependence disorders). Studies were selected to capture lifespan patterns and thus included participants ranging from childhood through older

adulthood. Included in the meta-analysis were peak voxel coordinates from published studies that compared a psychiatric group to healthy participants, which thus represented indicators of regional gray matter volume differences associated with that diagnosis. The final sample included nearly 200 peer-reviewed papers and 16,000 patients and matched healthy controls.

The revised activation likelihood estimation (ALE) algorithm was implemented to identify consistent patterns of gray matter differences between patients and controls across studies (Eickhoff et al., 2009, 2012). This algorithm aims to identify areas showing a convergence of reported coordinates across experiments higher than expected under a random spatial association.

Across all studies, the clear majority (85%) of peak voxels represented decreased gray matter in patients compared with controls. Consistent gray matter decreases in patients were found in the bilateral anterior insula, dorsal anterior cingulate (dACC) and dorsomedial prefrontal cortex (dmPFC), ventromedial PFC (vmPFC), thalamus, amygdala, hippocampus, superior temporal gyrus and parietal operculum. By contrast, gray matter increases in patients were found exclusively in the striatum. To hone the set of regions to those common to both psychotic and non-psychotic disorders, we performed a conjunction which revealed a more circumscribed, shared pattern of gray matter loss in the bilateral anterior insula and dACC (Fig. 1). Furthermore, presence of gray matter loss in one region predicted gray matter loss in the other regions (Robinson et al., 2010) suggesting that this gray matter loss might occur in a coordinated fashion across a structural network inclusive of these regions. By contrast, the gray matter increases in the striatum of patients were evident only in the psychotic disorders group.

As the psychotic versus non-psychotic distinction does not

account for more refined phenotypic differences, a follow-up analysis of the extracted per voxel probability of observing gray matter decreases in each of the three common regions (right and left insula, dACC) revealed similar magnitude effects across all non-psychotic diagnoses, as shown in Fig. 2. Schizophrenia spectrum disorders showed significantly greater reductions of gray matter volume in these regions relative to the non-psychotic disorders as a whole. Notable given the dramatic differences in psychotropic use patterns between psychotic and non-psychotic disorders, these effects were not accounted for by current medication usage. In summary, these results suggest that anterior insula and dACC gray matter loss represent a transdiagnostic neural abnormality, most pronounced in disorders prone to psychosis.

To assess whether cognitive control capacity may be determined, in part, by the structural integrity of this anterior insula/dorsal anterior cingulate–based network, we examined relationships between gray matter volume in these nodes in relation to neuropsychological performance. We utilized a dataset of 163 healthy adults from the BRAINnet database who had completed a computerized neurocognitive assessment battery that covered a broad range of basic and higher-level cognitive functions. As such, this served as a conservative test of whether reduced gray matter volume would predict behavioral variability/weaknesses even in the context of healthy cognitive functioning and mental wellbeing.

To reduce the array of tasks representing overlapping cognitive domains, we conducted principal components analysis, which yielded three principal components. Consistent with identification of an overriding cognitive control factor in latent variable analyses of cognitive performance data (Miyake et al., 2000), the principal component accounting for the most variance among test performance reflected general cognitive control (task switching, interference, inhibition, working memory, conflict). The second component reflected sustained attention (continuous performance task) while the third component reflected cognitive processing speed (choice reaction time, finger tapping).

We then regressed individual behavioral performance on each of these components with subject-specific gray matter volumes, measured using whole brain volume-corrected VBM. Lower gray matter across the three common gray matter loss regions predicted worse performance in terms of general cognitive control with a similar-direction trend for sustained attention, but no effect on processing speed (Fig. 3). Gray matter volume in primary visual

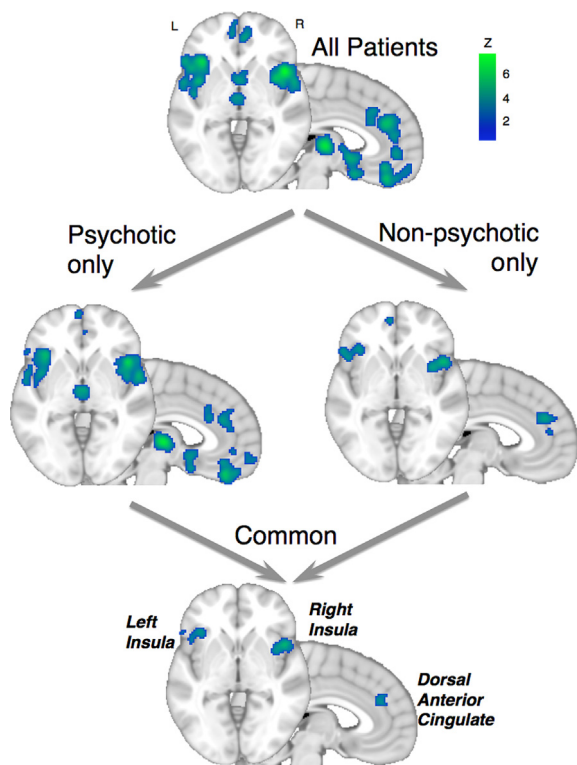


Fig. 1. Shared patterns of decreased gray matter from the voxel-based morphometry (VBM) meta-analysis. Patient versus healthy participant comparisons (a) for studies pooled across all diagnoses, (b) separately by psychotic or non-psychotic diagnosis groups, and (c) from a conjunction across the psychotic and non-psychotic diagnostic groups. Common gray matter loss is evident across diagnoses in the anterior insula and dorsal anterior cingulate (dACC). Adapted from Goodkind et al. (2015).

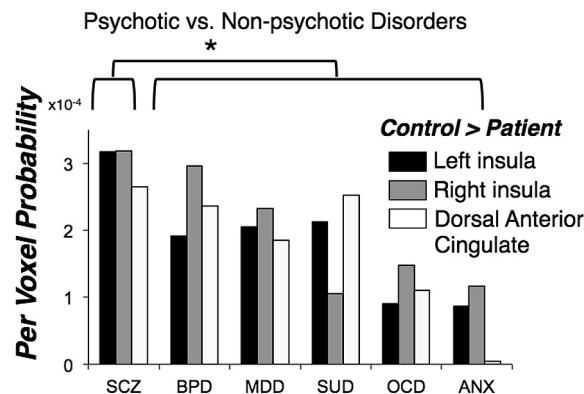


Fig. 2. Extracted per voxel probabilities of decreased gray matter in the VBM meta-analysis, separated by diagnosis and common gray matter loss region (left and right anterior insula, dACC). Values represent the probability of identifying a gray matter abnormality for an average voxel within the region of interest, derived from the modeled activation maps. SCZ = schizophrenia, BPD = bipolar disorder, MDD = major depressive disorder/dysthymia, SUD = substance use disorder, OCD = obsessive-compulsive disorder, ANX = anxiety disorders. Adapted from Goodkind et al. (2015).

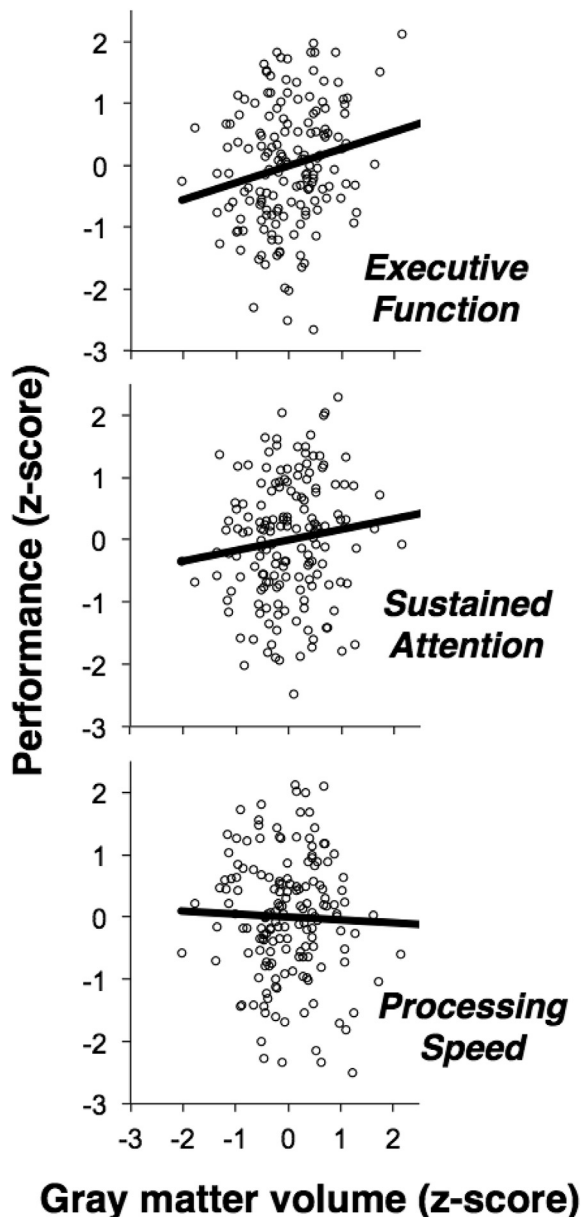


Fig. 3. Among 163 healthy participants from the BRAINnet Foundation Database who had completed a computerized neurocognitive assessment battery covering a broad range of basic and higher-level cognitive functions, lower gray matter across the three common gray matter loss regions (left and right anterior insula, dACC) predicted worse performance in terms of general executive function, with a similar trend for sustained attention, but no effect on general cognitive and performance speed.

cortex, a control region, was unrelated to any of the performance indices. These results suggest that lower gray matter in the common gray matter loss regions (i.e. more “patient-like” regional volume) is associated with worse higher-level cognitive control, but not with more rudimentary and less specific aspects of task performance.

In summary, in a VBM meta-analysis of nearly 16,000 patient and matched control participants, we identified a transdiagnostic pattern of gray matter loss in bilateral anterior insula and dACC. Further, lower gray matter volume in this network was systematically related to behavioral decrements on neuropsychological tasks—foremost for higher order cognitive control. Taken together,

these findings suggest a coordinated structural perturbation of this cingulo-opercular network across disorders, likely contributing to transdiagnostic cognitive control deficits.

1.4. A common underlying neurocircuit disruption: task activation

Unknown from our VBM meta-analysis is whether these nodes of common gray matter loss show parallel functional disruptions (Weinberger and Radulescu, 2016). A corresponding meta-analysis of cognitive control tasks is clearly warranted. In the interim, we examine the extant disorder-specific literature for evidence of abnormal activation in patients during cognitive control tasks. In short, we consider whether findings augur a common functional substrate of cognitive dyscontrol, which overlaps with the disrupted structural integrity of the anterior insula/dorsal anterior cingulate-based network.

Cingulo-opercular, Fronto-parietal & Multiple Demand Networks & Cognition. The insula and anterior cingulate (i.e., cingulo-opercular or “salience network”; Seeley et al., 2007) feature prominently in intact (Hayes et al., 2014) as well as disordered emotional responding (Etkin and Wager, 2007; Satterthwaite et al., 2015). Increasingly, however, anterior cingulate and insular cortices are recognized as more broadly deployed—assigning salience for the coordination of dynamic interaction of large-scale neural networks in response to contextual demands (Jiang et al., 2015; Medford and Critchley, 2010; Menon and Uddin, 2010; (Jiang et al., 2015; Medford and Critchley, 2010; Menon and Uddin, 2010; Power et al., 2013; Sridharan et al., 2008).

Specific to the critical role of the cingulo-opercular network in cognitive control is its coordination with the frontal-parietal network to function as a superordinate or “multiple demand” cognitive control/processing network (Duncan, 2010; Duncan and Owen, 2000; Müller et al., 2015). That is, in conjunction with the dACC (and the posteriorly adjacent medial frontal cortex) and bilateral anterior insula, a network of regions referred to as the fronto-parietal or central executive network (Dosenbach et al., 2008) are reliably recruited as part of the multiple demand network: the dorsolateral prefrontal cortex (dlPFC)/middle frontal gyrus, inferior frontal junction/gyrus, ventrolateral prefrontal cortex (vlPFC), inferior parietal cortex extending into intraparietal sulcus, and mid-cingulate cortex extending into pre-supplementary motor area (pre-SMA). An empirically derived multiple demand network is represented in Fig. 4. Müller & colleagues (2015) performed a conjunction across results from three large-scale meta-analyses of cognitive tasks in healthy participants, retrieved through ANIMA, a data sharing initiative (<http://anima.fz-juelich.de>). Identifying regions reliably recruited across diverse cognitive domains thus yielded the 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 and domains (Duncan, 2010). For example, the multiple demand network is activated in tasks ranging from performance monitoring, to focusing attention, to storing information in working memory, to inhibiting irrelevant information and selecting competing task-relevant responses (e.g., Fedorenko et al., 2013; Müller et al., 2015). Furthermore, the multiple demand network is sensitive to cognitive demand, showing activation proportional to increasing difficulty (Fedorenko et al., 2013). Importantly, the canonical pattern is observed not only at the single task level, but also the individual level, suggesting that the patterns observed at group (Duncan and Owen, 2000) and meta-analytic levels (Müller et al., 2015; Niendam et al., 2012) are not artifacts of aggregating findings.

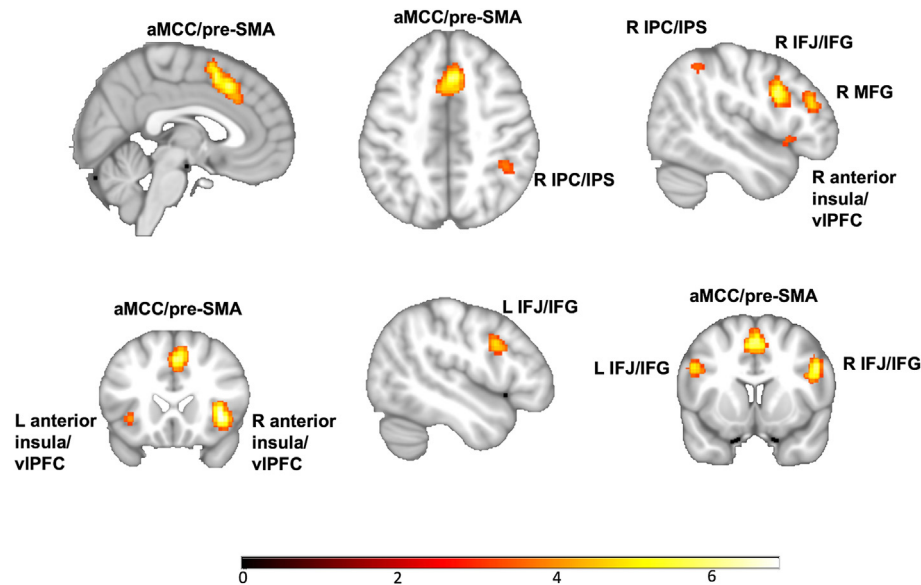


Fig. 4. The multiple demand network as empirically derived by Müller et al. (2015) from conjunction of results across three large-scale meta-analyses of diverse cognitive tasks in healthy participants (retrieved through ANIMA (<http://anima.fz-juelich.de>) (Reid et al., 2016)). aMCC/pre-SMA = anterior mid-cingulate cortex/pre-supplementary motor area; IPC/IPS = intraparietal cortex/sulcus; MFG = middle frontal gyrus; IFJ/IFG = inferior frontal junction gyrus; vIPFC = ventrolateral prefrontal cortex.

Although findings have been mixed in terms of which multiple demand network components show dissociable sensitivity to phasic (i.e., moment-to-moment) versus sustained (i.e., set maintenance) demands (e.g., Braver, 2012; Cole and Schneider, 2007; Crittenden et al., 2016; Dosenbach et al., 2006, 2008; Sadaghiani & D'Esposito, 2015; Wilk et al., 2012), accumulating findings suggest that the broad multiple demand network can be differentiated into subnetworks—a cingulo-opercular (CO) network and a frontoparietal (FP) network (Dosenbach et al., 2008) whose close coupling provides the foundation for a broad array of cognitive processes. Analyses of resting-state (Dosenbach et al., 2007) as well as cognitive task-based fMRI (Crittenden et al., 2016) have shown that while coordination is high across the broad network, nodes within the CO and FP subnetworks show stronger connectivity within than between subnetworks. Additionally lesions to nodes of one of the subnetworks hampers functional connectivity within that network, while integrity of the other network remains relatively preserved (Nomura et al., 2012). Recent work on causal interactions between these subnetworks during cognitive tasks (Cai et al., 2016; Chen et al., 2015; Jiang et al., 2015) suggests the anterior insula amplifies salience detection in the anterior and mid-cingulate in a manner proportional to both cognitive demand and individual capacity, and, in turn prompts activation of the broader frontal-parietal network, particularly lateral frontal regions (dlPFC/IFJ) and parietal cortex. Furthermore, Cieslik et al. (2002) performed a coactivation-based parcellation of the left lateral frontal cortex across cognitive paradigms. Two functional subregions emerged with the anterior region preferentially connected to the CO subnetwork-based anterior cingulate and the posterior region with the FP subnetwork-based intraparietal sulci. In summary, the cingulo-opercular and frontal-parietal subnetworks functionally integrate to subservise a wide array of cognitive functions as a coordinated, broader multiple demand network.

Mental Illness & the Multiple Demand Network. Next we consider the possibility that across disorders there is evidence of functional impairment in the multiple demand network, including dACC and anterior insula. Relative to other Axis I disorders and consistent with the severity of neurocognitive and functional

impairment, schizophrenia has received the most intensive examination of cognitive control/executive function neurocircuitry, including a handful of whole-brain meta-analyses. In the most recent, Minzenberg et al. (2009) analyzed functional magnetic resonance imaging and positron emission tomography findings from 41 studies of a broad array of tasks including delayed match-to-sample, delayed response, go/no-go, mental arithmetic, N-back, oddball, sequence recall, Stroop, Wisconsin Card Sort, and word generation tasks. Across tasks, patients showed pronounced hypoactivation relative to control participants in bilateral dlPFC, right vIPFC, visual, and right premotor cortices as well as inferior parietal lobule and medial frontal gyrus extending to dACC. Regarding subcortical regions, patient hypoactivation also occurred in the putamen and dorsomedial thalamus. In contrast, patient hyperactivation was observed in a more posterior region of the dACC extending to supplementary motor area. Increased mid-cingulate/pre-SMA among patients relative to control participants may reflect a compensatory process for maintaining intact performance amidst deficiencies in other multiple demand network nodes (i.e., adaptively balancing proactive versus reactive control; Jiang et al., 2015).

Very similar patterns of impairment seated within and extending beyond the multiple-demand network emerge in bipolar disorder, though with less pervasive disruption compared to schizophrenia. Wegbreit et al. (2014) implemented a whole-brain meta-analysis on 44 cognitive processing studies spanning numerous domains and tasks (e.g., stroop, n-back, go/no-go, paced motor task, sentence completion, delayed match-to-sample, stop signal). Patient hypoactivation emerged in bilateral inferior frontal gyrus/vIPFC, superior frontal gyrus, visual cortex, putamen, precuneus, lingual gyrus, and inferior parietal lobule. Patient hyperactivation was evident in pregenual ACC and mid-cingulate cortex (Chen et al., 2011). Underscoring the domain generality of these patterns, similar multiple demand network hypoactivation has been observed in meta-analyses of bipolar disorder circumscribed to episodic memory (Ragland et al., 2009) and response inhibition (Hajek et al., 2013).

Major depressive disorder also shows aberrant recruitment of

multiple demand network nodes, though even less extensive than bipolar disorder and consistent with the moderate effect sized neuropsychological deficits. In a whole-brain meta-analysis of 19 cognitive control tasks similar in domain and task breadth to the schizophrenia and bipolar studies reviewed previously, patients showed hypoactivation in right inferior frontal gyrus and left thalamus. Patient hyperactivation emerged in medial and bilateral middle frontal gyrus, putamen, and left thalamus (Palmer et al., 2015). A separate meta-analysis of working memory tasks in major depression, demonstrated lateral and medial prefrontal hyperactivation was attributable to patient samples showing worse performance and thus possibly reflects compensatory efforts (Wang et al., 2015). In sum, across psychotic, bipolar, and unipolar depression disorders, the extent of network deficits are on par with observed neuropsychological impairments.

Both anxiety disorders and substance use disorders have less often been the subject of functional neuroimaging investigation of cognitive control and meta-analytical summaries are as yet unavailable. In the case of anxiety disorders, the majority of whole-brain functional imaging studies of cognitive control tasks have focused on DSM-IV defined OCD and PTSD, paralleling the neuropsychological publication biases. A search in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) for whole-brain neuroimaging investigations of cognitive control/executive function tasks in anxiety disorders was performed. Specific search terms are provided in the supplemental materials. A total of 1469 articles were reviewed published through July 2016, revealing 29 studies with 35 tasks comparing neurocircuit activation during cognitive demand in patients compared to control participants. Twenty-one of these studies were of OCD, 7 of PTSD, and only one of generalized social anxiety disorder. Taken together, these anxiety disorders tended to show reduced lateral and medial prefrontal activation in tasks reflecting the canonical dimensions of shifting, inhibition, and updating (e.g., Chen et al., 2009; Falconer et al., 2008; Gu et al., 2008; Kang et al., 2013; Roth et al., 2007; Remijnse et al., 2013). In contrast, dACC/anterior insula involvement was alternately marked by hyper- (Fitzgerald et al., 2005; Maltby et al., 2005; Marsh et al., 2014; Roth et al., 2007) and hypoactivation (Chen et al., 2009; Gu et al., 2008; Kang et al., 2013; Remijnse et al., 2013) in different samples. The variability observed between these neuroimaging studies strongly underscores the need for additional investigations of cognitive control circuits in anxiety and related disorders, especially as PTSD, OCD, and traditionally defined anxiety disorders may be more heterogeneous than originally thought. In latent variable analysis of underlying symptom dimensions, no consensus has emerged regarding whether OCD and PTSD are better construed as predominantly fear or anxious-misery disorders (Cox et al., 2002; Forbes et al., 2010). Additionally, PTSD and OCD were reclassified from anxiety disorders into separate spectra in DSM-5, Trauma and Stress-related Disorders and Obsessive-Compulsive and related disorders, respectively. This latter DSM revision suggests a particular paucity of data on contemporary nosologically defined anxiety disorders.

Similar to anxiety disorders, the literature on substance use disorders and functional cognitive control circuits suffers from a limited corpus and pronounced disorder heterogeneity. For example, central nervous system effects and neurotoxicity vary dramatically across substance(s) of abuse. The same PubMed search run for anxiety disorders was repeated for substance use disorders (see supplement for details). A total of 1182 articles published through July 2016 were reviewed, revealing 37 studies comparing neurocircuit activation during cognitive functioning in patients compared to control participants. These studies included stimulant ($n = 13$), alcohol ($n = 10$), cannabis ($n = 6$), polysubstance ($n = 4$), opiate ($n = 3$), and cocaine ($n = 1$) abuse/dependence also varying

in terms of active or abstinent users. Despite the variability in identified substances of use and abuse, these patients relative to other disorders tended to show more uniform attenuations of the multiple demand network and related regions (e.g., Akine et al., 2007; Bach et al., 2012; Bolla et al., 2003, 2005).

Structure, Function, & the Multiple Demand Network. In summary, in a prior meta-analysis we observed reduced gray matter in the anterior dACC and bilateral anterior insula across disorders. The cingulo-opercular (CO) network, a key subnetwork of the broader multiple demand network whose efficient deployment is essential for intact cognition, comprises these regions. A review of functional neuroimaging studies of cognitive control tasks across disorders suggested a functional parallel. That is, regions of both the CO and FP subnetworks of the multiple demand network were implicated in transdiagnostic cognitive control deficits. Consistent with the essential role of anterior insula as neural network switchboard coordinating large-scale network interactions, weakening of the structural integrity of this CO network would likely affect a multitude of processes, possibly contributing to the wide array of cognitive as well as affective dysfunction and symptom presentations in mental illness. Additionally, large-scale structural and functional connectomics have demonstrated that many of the multiple demand network nodes implicated in psychiatric cognitive dysfunction serve as densely interconnected hubs. These hubs, namely superior frontal cortex, superior parietal cortex, and the insula (as well as bilateral precuneus, hippocampus, putamen and thalamus) form a central core or “rich club” (e.g., van den Heuvel and Sporns, 2011) undergirding information transfer and integration. In fact, direct comparisons of connectomics in schizophrenia patients and control participants has shown reduced density of rich club connections predominantly comprising the white matter pathways that link multiple demand network nodes, specifically the midline frontal, parietal, and insular hub regions (van den Heuvel et al., 2013). In essence aberrations in gray matter, functional activation and white matter connections likely interact to prompt the real-world impairment secondary to transdiagnostic neurocognitive impairment and affective distress.

2. Summary, limitations, & future directions

Accumulating findings have revealed that psychiatric disorders share a common factor or vulnerability to dysfunction. Similarly, historic conceptualizations of distinct cognitive domains have been superseded by models that include a higher order common cognitive control/executive function factor. Separate studies suggest this common cognitive control factor may be related to deficits in a frontal-cingulate-parietal-insular network recruited for a wide diversity of cognitive demands. Additionally, the nodes in this multiple demand network (dACC and insula), which function as a switchboard for communication between large-scale networks, share a common vulnerability to gray matter reduction, more pronounced at extreme levels of general psychopathology.

While burgeoning evidence of common factors calls into question historic parcellations of cognition and disease, it is important to note that shared variance also reflects the inherent impurity in real world psychiatric distress and cognitive processing. For example, a bias for domain generality over specificity in brain function and behavior may in part reflect that study tasks are grouped into domains based on conceptualizations of the predominant underlying executive function. Naturally, however, performance of most tasks involves a synergy of cognitive processes that spans domains such as working memory, set shifting, and performance monitoring. In a related vein, robust transdiagnostic effects in part reflect that polythetic diagnostic schemes, which yield tremendous phenotypic heterogeneity, in combination with

high comorbidity hamper detection of profiles specific to putatively “pure” disorder manifestations. Finally, it must be noted that both the corpus of task-based functional imaging and performance data on cognitive control is particularly limited for some individual disorders and cognitive domains, which biases findings towards common over distinct deficits. For example, among healthy control samples updating- and shifting-specific factors emerge with the common cognitive control factor (Miyake and Friedman, 2012). The emerging pattern of transdiagnostic neurocognitive and multiple demand network impairment does not preclude the presence of distinct deficits within individual disorders and individual brain regions. The appearance of common impairment could result from numerous distinct deficits. Elucidating this point necessitates more extensive investigation across disorders and across task domains to enable more powerful analyses of concurrent specific and common deficits in brain and behavior. In fact, future studies examining a single disorder focused on a single potential marker of executive function impairment would likely provide little to advance our understanding of neurocognitive impairments in mental illness.

Taken together, large-scale investigations that enable dimensional factor analysis of common and specific symptom and neurocognitive domains in conjunction with multivariate analysis of brain activation/deactivation patterns are warranted. At the forefront of this work and an exemplar for future investigations, Shanmugan et al. (2016) performed such an approach on data from a community sample of 1129 individuals who completed a working memory task during fMRI acquisition. Severity on a general psychopathology factor reliably predicted attenuated recruitment of the multiple demand network. Symptom factors reflecting lower order dimensions were also considered. That is, psychosis spectrum symptoms were associated with hypoactivation of the dlPFC, externalizing symptoms with hypoactivation of the frontoparietal cortex and cerebellum, and anxious-misery symptoms with widespread hyperactivation of the executive network. Essentially, common and specific factors demonstrated dissociable patterns, which would have been obscured in a conventional nosological framework. While additional transdiagnostic investigations that enable more comprehensive latent variable modeling of common as well as potential distinct impairments are needed, findings to date of common factors across symptom, behavior and brain modalities have been robust and most importantly, have shown prospective prediction of distress and functional impairment that often exceed traditional “distinct” factors.

3. Conclusions

Consistent with principles of the Research Domain Criteria (RDoC) project (Kozak and Cuthbert, 2016), the current review implicates disruption of a cognitive control network across disorders. Importantly, this network parallels the multiple demand network intrinsic to adaptive, flexible cognition. Given our prior findings of transdiagnostic gray matter loss in overlapping regions of this network, a parallel is suggested across structural and functional measures of brain dysfunction. Also highlighted is the particular vulnerability of the anterior cingulate and insular cortices to perturbations especially in the context of highly burdensome general psychopathology. Most importantly, these findings signify promise for psychosocial, pharmacological, and neuromodulatory interventions that target the foundation of intact, dynamic cognition seated in the frontal-cingulate-parietal-insular network. Such targeted approaches could be powerful for ameliorating not only symptoms, but also the broad functional impairments and diminished quality of life prevalent across psychiatric disorders.

Conflict of interest

The authors declare no competing financial interests relevant to this research.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jpsychires.2016.08.001>.

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