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Evoking network profiles of the dorsal anterior cingulate in youth with Obsessive-Compulsive Disorder during motor control and working memory

Thomas D. Meram[1], **Asadur Chowdury**[1], **Philip Easter**[1], **Tyler Attisha**[1], **Ellanya Kallabat**[1], **Gregory L. Hanna**[2], **Paul Arnold**[3], **David R. Rosenberg**[1], **Vaibhav A. Diwadkar**[1]

[1]Department of Psychiatry and Behavioral Neurosciences, Brain Imaging Research Division, Wayne State University School of Medicine, 3901 Chrysler Service Dr Suite 5B, Tolan Park Medical Bldg, Detroit, MI 48201, USA

[2]Department of Psychiatry, University of Michigan, 4250 Plymouth Rd, Ann Arbor, MI 48109, USA

[3]Department of Psychiatry & Medical Genetics, University of Calgary, 3280 Hospital Dr NW, Calgary, AB T2N 4Z6, Canada

Abstract

Interest in Obsessive-Compulsive Disorder's pathology has focused on brain network profiles of the dorsal Anterior Cingulate Cortex (dACC), given its role as a principal control region. Both motor control and working memory tasks induce dysfunctional dACC profiles in OCD, and here, we contrasted dACC network profiles in OCD and age-comparable controls during both tasks (from data collected in the same participants). The motor task required participants to tap their right forefinger in response to a flashing white probe; the memory task was a standard n-back (2-Back) that required participants to identify if a current stimulus was identical to the one presented two items before it in the sequence. Network interactions were modeled using Psychophysiological Interactions (PPI), a model of directional functional connectivity. Our inter-group analyses indicated a) that the motor control task evoked greater dACC modulation

Corresponding Author: Vaibhav A. Diwadkar, Ph.D. vdiwadka@med.wayne.edu, Professor, Dept. of Psychiatry & Behavioral Neurosciences, Co-Director, Brain Imaging Research Division, Wayne State University School of Medicine, Suite 5B, Tolan Park Medical Building, 3901 Chrysler Service Drive, Detroit, MI 48201, U.S.A.

Author Statement

TM conducted the analyses, created the figures and wrote the paper
AC assisted in analyses and statistical methods
PE assisted in data collection and clinical analyses
TA assisted in data analyses
EK assisted in data analyses
GH assisted in clinical characterization and data collection
PA assisted in clinical issues and data collection
DR assisted in clinical characterization and data collection
VAD oversaw all aspects of the analyses, writing and presentation

Conflict of Interest

The authors declare no conflicts of interest.

than the working memory task, and b) that the modulatory effect was significantly greater in the OCD group. We also investigated the relationship between OCD symptom dimensions (lifetime obsession and lifetime compulsion measured using the CY-BOCS) and dACC network profiles in OCD. This regression analysis revealed a dichotomy between Obsessive-Compulsive symptom dimensions and the degree of dACC modulation: it was primarily increased obsessions that predicted increased modulation during the motor control task, but primarily increased compulsions that predicted increased modulation during the working memory task. These results re-emphasize the salience of the dACC in OCD, and the primacy of tasks of motor control in evoking dACC pathology in the disorder.

Introduction:

Obsessive-Compulsive Disorder (OCD) is a neuropsychiatric disorder characterized by intrusive, anxiety provoking thoughts and urges (obsessions), and repetitive behaviors performed to reduce anxiety (compulsions) (Abramowitz et al., 2009). OCD is prevalent in youth, with one-year incidence rates in sub-clinical and clinical adolescent populations estimated at 8.4% and 0.7% respectively (Valleni-Basile et al., 1996). Approximately 45% of adolescents report OCD symptoms (Apter et al., 1996; Berg et al., 1988). Despite relatively high frequencies of occurrence, understanding patterns of task-induced network dysfunction in the brain's pathways has proven challenging. OCD's complex symptoms have been linked to an inability to disengage intrusive thoughts from eliciting behavior, implying a pathology that increases inhibitory control (Bari and Robbins, 2013; Chamberlain et al., 2005; Fineberg et al., 2014; Lipszyc and Schachar, 2010; van Velzen et al., 2014), a pattern highly suggestive of aberrant functioning of brain networks that sub serve control processing (Piras et al., 2013).

Salient aspects of OCD pathology suggest that the dorsal Anterior Cingulate Cortex (dACC) is of particular structural and functional interest (Diwadkar et al., 2015). This region plays a prominent role in cognition, attention, and motivation (Bush et al., 2002; To et al., 2017; van Veen and Carter, 2002). Neuroimaging studies indicate that it is typically engaged during response conflict (occurring between incompatible streams of information processing) (Botvinick et al., 2001) and performance monitoring (Gilbert et al., 2018; Shenhav et al., 2013; van Veen and Carter, 2002). The literature on the role of the dACC in conflict processing is substantial (Nakamura et al., 2005), but through its mediation of multiple brain networks, the dACC has also been implicated as a principal control region associated particularly with motor and memory control (Paus, 2001). The anatomy of the dACC interjects heavily with networks for motor control (Stevens et al., 2011), providing a) a structural bases for the direct modulation of motor networks (Asemi et al., 2015) and b) a link between sensorimotor and cognitive processing (Friedman et al., 2017). In addition, through its connections to the prefrontal cortex (Stevens et al., 2011), the dACC functions as a regulator of executive processes including decision making and working memory (Lenartowicz and McIntosh, 2005). This interface with regions implicated in the maintenance and manipulation of mnemonic representations suggests that the dACC is part of a general control system that coordinates processes during working memory (Chafee and Goldman-Rakic, 2000; Chein and Schneider, 2005; Koenigs et al., 2009; Mars and Grol,

2007; McCarthy et al., 1997). Indeed, executive control *is* central to performance during tasks such as working memory, as such tasks induce varying demands, require constant encoding and updating of stimuli, resulting in a substantial propensity for errors (Bakshi et al., 2011; Diwadkar et al., 2015; Diwadkar et al., 2011). Here, the established role of the dACC in error monitoring during conflict assumes significance (Bakshi et al., 2011; MacDonald et al., 2000; Schulz et al., 2011), as demanding task characteristics elevate the role of regions such as the dACC during tasks that elicit a high degree of control.

Previous studies in OCD have demonstrated that dACC network profiles significantly differ from those of healthy controls during motor (Friedman et al., 2017) and mnemonic tasks (Diwadkar et al., 2015), where in both task domains, OCD were characterized by exaggerated modulation by the dACC. This exaggerated modulation suggests that the obsessive dimension of the illness may alter dACC function so as to induce exaggerated control of motor and memory networks (Diwadkar et al., 2015; Li and Mody, 2016). Task complexity in and of itself does not explain these effects as employed motor paradigms are generally more tractably performed than working memory tasks (Diwadkar et al., 2017; Diwadkar et al., 2018).

Clearly *both* working memory and motor function can evoke dACC-related network pathology in OCD, though in principle, the dACC is purported to play slightly different roles in each domain. Despite this general understanding, the *relative* degree of dACC dysfunction in OCD evoked by tasks of motor control versus tasks of working memory remains unclear. Understanding whether one or the other task domain is more evocative of network dysfunction will be informative about the interjection between task demands and dACC dysfunction, something that in turn will be an effective means for discovering network pathology in OCD. Moreover, exploratory analyses of the relationship between OCD symptom dimensions and the degree of (any) dACC dysfunction will provide a measure of support for how aspects of the illness are linked with evoked dACC function in each domain.

Thus, our primary aim was to discover relative dysfunction associated with dACC network profiles across these two task active states. To achieve this, we modeled and analyzed dACC network profiles under two specific experimental paradigms acquired in the same participants and the same imaging session; motor control, induced using an established visuo-motor integration paradigm (Asemi et al., 2015; Diwadkar et al., 2015; Friedman et al., 2017; Morris et al., 2018) and working memory, induced using a standard verbal n-back task (Casey et al., 1995; Diwadkar et al., 2017; Diwadkar et al., 2015; Diwadkar et al., 2011).

Methods:

Subjects

Twenty-eight participants with a diagnosis of OCD and twenty-seven healthy controls (HC) participated in the fMRI study (Refer to Table 1 for demographic data). Participants and parents were interviewed with the Schedule for Obsessive-Compulsive and Other Behavioral Syndromes and Schedule for Schizophrenia and Affective Disorders for School-Aged

Children-Present and Lifetime Version (Kaufman et al., 1997; Wolff and Wolff, 1991). The lifetime (maximum) and current severity of OCD were assessed with a modified version of the Children's Yale-Brown Obsessive-Compulsive Disorder Scale (CY-BOCS) (Goodman et al., 1989; Scahill et al., 1997). Lifetime and current Axis I diagnosis were independently confirmed by clinicians (DRR, GLH), using DSM-5 criteria. Exclusion criteria included lifetime history of schizophrenia, other psychotic disorder, bipolar disorder, substance abuse or dependence, anorexia nervosa, bulimia nervosa, epilepsy, head injury with sustained loss of consciousness, Huntington's disease, dyskinesia, autism, IQ ≤ 80, or ≥ 15 on the lifetime version of the Social Communication Questionnaire (Mulligan et al., 2009; Rutter et al., 2003). The study was approved by the Wayne State University School of Medicine and the UM Human Investigation Committee. Legal guardians and participants provided written informed consent prior to participating in the study.

fMRI

Gradient echo EPI fMRI data acquisition was conducted at the Vaitkevicius Magnetic Resonance Center (WSU) on a 3T Siemens Verio system using a 12-channel volume head coil (TR: 2.6s, TE: 29ms, FOV: 256×256mm^2, acquisition matrix: 128×128, 36 axial slices, voxel dimensions: 2 × 2 × 3mm). In addition, a 3D T_1-weighted anatomical MRI image was acquired (TR: 2200ms, TI: 778ms, TE: 3ms, flip-angle=13°, FOV: 256×256mm^2, 256 axial slices of thickness = 1.0mm, matrix=256×256). A neuroradiologist reviewed all scans to rule out clinically significant abnormalities.

Uni-Manual Motor Paradigm

The established uni-manual motor task (Asemi et al., 2015; Diwadkar et al., 2017; Friedman et al., 2017; Morris et al., 2018) required participants to tap their right forefinger to a flashing white probe presented at different frequencies (.5 Hz or 1 Hz) and with different stimulus onset asynchronies (SOA). Periodic epochs (fixed SOA) allowed participants to establish and maintain a motor set. The SOAs for Random epochs were generated by pseudo-randomly sampling values from Gaussian distributions (μ = 1.0/2.0 s; σ = 0.5/1.0 s). The SOA lower bound was set at 300 ms (to exceed the lower limit of response latency). This condition preempted formation of a motor set, eliciting reactive responding. The number of elicited responses was held constant across all Periodic and Random epochs. Participants alternated between tapping and rest epochs each lasting 30 s (four epochs for each tapping condition and two rest epochs). Epochs were interspersed with short (10 s) rest intervals. Tapping responses were collected from the surface of a response touchpad (Current Design Systems, Inc.).

Working Memory Task Paradigm

During an established verbal working memory paradigm (n-back task) (Casey et al., 1995; Diwadkar et al., 2017; Diwadkar et al., 2015; Diwadkar et al., 2011), participants were presented with a sequence of letters indicating if the current letter was identical to the one present “n” stimuli previously in the sequence. Subjects responded via a two-choice button unit. Working memory load was varied (n=0 or n=2). Each condition lasted 30 s (presentation time: 500 ms; SOA: 2500 ms; 10 letters per condition) interspersed with rest epochs (20 s).

fMRI Processing

fMRI images were preprocessed and analyzed using SPM 12 (Statistical Parametric Mapping, Wellcome Department of Imaging and Neuroscience, London, UK) using standard processing methods. Spatial pre-processing included manually orienting images to the AC-PC line, correcting for head movement by aligning images to a reference image, and co-registering images to a high-resolution T_1 image which was normalized to the Montreal Neurological Institute template brain. Images were subsequently resliced into 3.375 mm^3 voxels (1.5 mm × 1.5 mm × 1.5 mm). A low pass filter (128 s) was used to remove low frequency components and a Gaussian filter was used to spatially smooth all images (8 mm full-width half maximum; FWHM). An autoregressive AR(1) model was used to account for serial correlation, and regressors modeled as box-car vectors (for each task-related condition) were convolved with a canonical hemodynamic reference waveform.

Brain network interactions were modeled using psycho-physiological interaction (PPI), a technique utilizing the general linear model to investigate functional connectivity by assessing modulatory effects of a seed region in a task active state (Friston et al., 1997; O'Reilly et al., 2012; Silverstein et al., 2016). PPI analyses were conducted for each task and subject using a seed (maximal response) in the dACC.

First level analyses modeled the degree of dACC modulation in each of the two task-active states. Time series from the dACC were extracted for all subjects using the effects of interest contrast of each task, and subsequently convolved with the corresponding task-active conditions. Thus, for working memory, analyses were conducted across all 2-back epochs, and for motor control, across all the periodic and random epochs. This approach allowed us to estimate veridical profiles associated with each of the working memory and motor control domains. The resulting interaction terms were positively weighted (O'Reilly et al., 2012). Thus, each participant contributed two first-level PPI maps (one per task) to subsequent 2^{nd} level analyses. The 2^{nd} level analysis utilized a two-factor design with Group (OCD vs. HC) as independent factor, and Task (Memory vs. Motor) as non-independent factor. This design structure flexibly allowed us to model effects associated with Group (OCD ≠ HC) and Task (Motor ≠ Memory). For all contrasts, significant clusters were identified using 10^4 Monte Carlo probability simulations of the data ($p<.05$ cluster level) which compute the probability of a random field of noise (after spatial correlations of voxels based on image smoothness are accounted for). These simulations generate a minimum cluster size threshold for significance after thresholding noise to a certain level (Morris et al., 2018). Therefore, our analysis used both individual voxel thresholding and a minimum cluster size thresholding. The statistical approach is based on an underlying and tenable assumption that activation occurs over contiguous voxels while noise does not aggregate in clusters (Ward, 2000).

Results:

Results are organized to present evidence of (1) dysfunctional dACC network profiles in OCD, (2) differences in network profiles between tasks, and (3) correlations between OCD symptom dimensions and the degree of dACC network dysfunction.

Group Related Effects on dACC Modulation

Figure 1 depicts clusters under the effect of Group (OCD ≠ HC) in each of the Motor and Memory task paradigms. Clusters depict regions characterized by differential modulation by the dACC.

OCD were characterized by significantly *greater* dACC modulation under both experimental paradigms, with minimal effects observed in the opposite direction (HC > OCD). This hyper-modulation was particularly salient for the motor task (Figure 1A). During the motor task, OCD were characterized by increased dACC modulation of multiple targets, including the Superior and Middle Occipital Lobules, Precuneus, Cuneus, Insula, Pre- and Post-Central Gyri, Frontal Gyrus, and the Superior Parietal Lobule. More circumscribed effects were observed for the memory paradigm (Figure 1B). Here, effects were observed in areas including Precuneus, Cuneus, Frontal Gyrus, Superior and Middle Occipital Lobules, and the Supramarginal Gyrus (Table 2 reports significance under the Effect of Group).

Task Related Effects on dACC Modulation

Figure 2 depicts significant clusters of differential dACC modulation between the Motor and Memory task paradigms in OCD and HC groups.

In both groups, the motor task induced *greater* dACC modulation than working memory. This effect (Motor > Memory) was more salient in OCD patients, observed in areas including the Precuneus, Cingulum, Superior and Middle Occipital Lobe, Pre- and Postcentral Gyri, Inferior Parietal Lobule, and Frontal Gyrus in OCD (Figure 2A). In HC, Motor > Memory targets included the Precuneus, Cingulum, Angular Gyrus, and Inferior Parietal Lobule for HC (Figure 2B, Table 3 reports significance under the Effect of Task).

Regression Analyses

In clusters under the group effect (OCD ≠ HC; Figure 1), did OCD symptom dimensions predict the degree of dACC modulation? To examine this question, regression analyses were employed to investigate how dACC modulation scaled as a function of two covariates of clinical interest: Lifetime Obsession and Lifetime Compulsion symptom scores measured using the CY-BOCS (see Methods). The 1st level PPI maps of each subject (Motor, Working Memory) were submitted to separate regression analyses with Obsession and Compulsion scores employed as regressors of interest. Resulting analyses were masked using significant clusters under the Effect of Group (Figure 1). This approach allowed us to specify whether clusters under the group effect were predicted by the dimensions of Obsession and/or Compulsion.

Significant clusters are depicted in Figure 3. For ease of access, clusters significantly and uniquely predicted by Compulsions are rendered in green (Compulsions Only), while those significantly and uniquely predicted by Obsessions are rendered in red (Obsessions Only). Clusters significantly predicted by *both* Obsessions and Compulsions are rendered in yellow (Compulsion ∩ Obsession).

Positive Relationships between symptom dimensions and the degree of PPI modulation:

Obsessions and Compulsions both exerted strong positive effects on dACC modulation, but the effects were confounded by task. Thus, Obsessions predicted increases in dACC modulation during the motor task, but Compulsions predicted increases in dACC modulation during the memory task (thus, Figure 3A is characterized by more red clusters, whereas Figure 3B is characterized by more green clusters). These effects were observed in areas including the Postcentral, Middle Frontal, and Supramarginal gyri (Obsessions, Motor Control; Figure 3A) and the superior occipital lobule, Precentral and Postcentral gyri (Compulsions, Working Memory; Figure 3B).

Negative Relationships between symptom dimensions and the degree of PPI modulation:

Obsessions and Compulsions both exerted strong negative effects on dACC modulation, but here too, effects differed by task. For the motor task, *both* Compulsions and Obsessions predicted decreases in dACC modulation. However, for the memory task it was primarily Compulsions that predicted a decrease in dACC modulation (thus, Figure 3C is characterized by both red and green clusters, whereas Figure 3D is characterized by more red clusters). For the motor task, increases in Obsessions predicted decreased dACC modulation of the Inferior frontal operculum and Angular gyrus (Obsessions, Motor Control; Figure 3C), while increases in Compulsions predicted decreased dACC modulation in the Rolandic operculum and Supramarginal gyrus (Compulsions, Motor Control; Figure 3C). For the memory task, increases in Obsessions predicted decreased dACC modulation of the Insula and Superior frontal gyrus (Obsessions, Working Memory; Figure 3D).

Discussion:

We assessed differences in dACC network profiles in OCD and HC, induced by simple motor control or working memory. Our principal results were these: a) Regardless of group, the dACC's modulatory influence during motor control *exceeded* that induced during memory (Figure 2); b) For *both* motor control and working memory, OCD were characterized by significantly *greater* modulation by the dACC, with effects particularly salient during motor control (Figure 1); and c) Obsessive and Compulsive symptom dimensions predicted the degree of dACC network dysfunction in each experimental paradigm (Figure 3), but in complementary ways. During motor control, it was obsessive symptoms that were more predictive (Figure 3A), whereas during working memory, it was compulsive symptoms that were more predictive (Figure 3, B). Below we comment on how these results further elucidate the role of the dACC in the pathology of OCD, and how our results inform the experimental neuroscience of OCD.

The role of the dACC in control and performance monitoring

Previous investigations of brain activity during simple motor control and working memory have provided a rich window for exploring dACC network profiles (Bakshi et al., 2011; Diwadkar et al., 2015; Friedman et al., 2017; Weiss et al., 2018) that in part represent functional expressions of the region's structural connectivity (Paus, 2001). Anatomical studies of the dACC note connections to areas associated with motor control including the motor cortex, premotor cortex, and spinal cord (Heilbronner and Hayden, 2016). In

addition to the significant connections with motor areas, the dACC also interjects heavily with areas associated with emotion, including the amygdala, and areas associated with executive control, such as the prefrontal cortex (Stevens et al., 2011). The dACC's functional position primes it to receive incoming sensory information, and then act on downstream motor regulation (Asemi et al., 2015; Morecraft et al., 2012). Thus, the structure is ideally positioned to translate intentions to actions, placing a heavy emphasis on the link between cognition and motor responses (Paus, 2001). Thus, the anatomy of the dACC, particularly its associations with motor areas, supports its integral role in the control and monitoring of motor function (Diwadkar et al., 2015; Friedman et al., 2017; Paus, 2001).

In addition to its role in motor control, the dACC is also associated with cognitive control and performance monitoring (Botvinick, 2007; Botvinick et al., 2001; Heilbronner and Hayden, 2016; Holroyd and Yeung, 2012). Cognitive control is generally defined as the ability to attend to relevant information while disregarding irrelevant information (Braver, 2012; McGovern and Sheth, 2017; Mennigen et al., 2014), though at the level of network interactions, it can be more generally related to how apex regions like the dACC exert effects on other regions (Breukelaar et al., 2016; Diwadkar et al., 2017; Schulz et al., 2011). Recent investigations have indeed suggested that the dACC may be biased towards motor control. For example, the dACC selectively modulates the Supplemental Motor Area (SMA) during visually-coordinated uni-manual behavior, but *not* during working memory (Diwadkar et al., 2017). Such results suggest that the dACC selectively potentiates motor sub-networks during simple motor tasks, an idea consistent with our results where within the healthy control group, dACC modulation during the motor task significantly exceeded that observed during working memory. Studies also implicate the dACC in performance monitoring, suggesting that the structure serves as to monitor both error (Holroyd and Coles, 2002) and conflict (Botvinick, 2007; Botvinick et al., 2001; Kerns et al., 2004; van Veen and Carter, 2002) in a continuous manner (Blanchard et al., 2015; Carter et al., 1998; Holroyd and Coles, 2002). Notably all these purported functions of the dACC interject with aspects of OCD pathology.

The dACC in Obsessive-Compulsive Disorder

An extensive literature implicates the dACC in the etiology of OCD (McGovern and Sheth, 2017; Wang et al., 2017; Zhang et al., 2017) with multiple theories speculating on the region's contribution. A prevailing theory proposes that normative functional loops associated with cortico-striato-thalamo-cortical (CSTC) circuits are dysfunctional in OCD, in part because of altered "bottom-up" thalamic inputs *and* altered dACC-related top-down control (Ahmari et al., 2014; Alexander et al., 1986; Goodman et al., 2014; Rajendram et al., 2017; Wang et al., 2017). Thus, the unique role of the dACC in cognition and performance monitoring assumes significance in OCD, as the disorder has been characterized by impairments in both domains. For example, Cocchi and colleagues used a Multisource Interference Task (validated task for cognitive control) to investigate functional network correlates of performance on goal-directed cognitive control (Cocchi et al., 2012). They observed significant functional differences between the OCD and control group, reporting both relative increases and decreases in regional connectivity.

Complementary theories on dACC function have highlighted its particular role in error-monitoring (Holroyd and Coles, 2002; van Veen and Carter, 2002), suggesting that the structure uses past action outcomes to inform current action selection (Egner, 2009; Rushworth et al., 2004). OCD subjects show increased error-related negativity implying that the disorder is characterized by overactive error-monitoring (Endrass and Ullsperger, 2014; Gehring et al., 2000; Grutzmann et al., 2016; Ullsperger et al., 2014). Recent accounts also suggest that in OCD, aberrant dACC network profiles may result from its inability to differentiate task-relevant from task-irrelevant information, an inability that leads to poorly specified control signals (McGovern and Sheth, 2017). Aberrant dACC signals may then act on downstream targets that include motor areas such as the pre-SMA, and SMA, and the thalamus (Diwadkar et al., 2017; Egner, 2009; Stevens et al., 2011), and these aberrant signals are coupled with (or drive) OCD-like symptoms.

Obsessive-Compulsive symptom dimensions predict dACC dysfunction in each task domain

"Parsing" OCD by its symptom dimensions enabled us to study how specific dimensions within OCD influence dACC pathology during motor control and working memory tasks. Studies have previously shown that anterior cingulate gray matter is robustly related to obsessive but not compulsive, symptom severity (Rosenberg and Keshavan, 1998; Szeszko et al., 2004) though such structural findings are not entirely consistent (Piras et al., 2013; Szeszko et al., 1999). For example, other studies, while not observing the supposed relationship between cingulate grey matter and symptom severity, have noted that specific OCD clinical features are related to microstructural alterations in projection and association fibers to posterior brain regions (Piras et al., 2019). Such microstructural alterations may result in deficits in executive processes, including those which the dACC is purported to play a role in. These in turn may evince some form of a parametric relationship to symptom dimensions. Of course, attempts to relate clinical dimensions to any form of underlying neuroimaging measure (whether functional or structural) are highly valuable and of substantial clinical relevance (Thorsen et al., 2018), but unfortunately are characterized more by hetero-, rather than homogeneity across studies (Begue et al., 2020). This may reflect on the complexity of clinical syndromes *and* the indeterminacies associated with *in vivo* neuroimaging data, and there may not be a straightforward solution. Nevertheless, our *specific* observations in this regard are somewhat compelling.

The motor task we employed was relatively simple and primarily reactive. Conversely, the working memory task was more deliberative and cognitively demanding. The resultant dichotomy between obsessive and compulsive symptom dimensions and complementary relationships to each of the tasks interject with the task elements. Thus, an increase in *obsessive* symptoms (defined as persistent, intrusive, and/or uncontrollable thoughts or urges) predicted increased dACC modulation during the reactive motor control task, but a *decrease* in obsessive symptoms predicted decreased dACC modulation during the working memory task. This dissociation was preserved when assessing the relationship to compulsive symptoms. Thus, an increase in *compulsive* symptoms (repetitive and ritualistic behaviors and/or thoughts performed to reduce anxiety) predicted increased dACC modulation during the deliberative and challenging working memory task. The link with anxiety is compelling

because anxiety and affect lead to competition with or inference on task-related processes (Eysenck and Calvo, 1992; Eysenck et al., 2007; Soloff et al., 2017; Soloff et al., 2015). Moreover, meta-analyses that studied the relationship between working memory capacity and anxiety, showed that measures of anxiety are significantly correlated with lower working memory capacity across tasks of varying complexity (Moran, 2016). By comparison, the obsessive dimension is most saliently related to the inability to control intrusive thoughts and urges (Norman et al., 2019).

As noted, aberrations in control is a common theme in the OCD literature and implicates the dACC in OCD pathology (Botvinick, 2007; Heilbronner and Hayden, 2016). Therefore, we would expect that aberrations in dACC network profiles during tasks that feature a high demand for cognitive control would be related to obsessive symptom severity. Indeed, it is precisely this correlation that was saliently observed during the motor task. The motor task is noted for relatively frequent response demands to visually presented stimuli. Both task conditions (periodic and random responding) featured higher *response frequencies* than did the working memory task. The expectation is that this difference in the frequency of responses led to greater response demands per unit of time, though other sub-demands would also be at play. During random epochs, the task structure induced a high propensity for false alarms and misses, plausibly evoking a greater degree of error and performance monitoring. By comparison, periodic epochs evoked the implicit perception of a temporal task structure. Thus, in OCD we found greater dACC modulation of regions associated with motor timing (the frontal gyrus, insula, and parietal cortex) (Laje et al., 2011; Paton and Buonomano, 2018) (Figure 1; Table 2).

Abnormalities in volitional motor control are strongly implicated in OCD (Takashima et al., 2019), and are almost certainly an expression of the generalized cortico-striatal dysfunction that characterizes many adolescent-onset psychiatric conditions (Kuo and Liu, 2019). Thus it is unsurprising that motor dysfunction is considered a proximal cause of various pathophysiological pathways and symptom expressions of psychiatric disorders (Hirjak et al., 2018). Considered in totality, it appears that the characteristics of our employed motor task evokes a more salient demand for control than evoked during the working memory task. Therefore, more prominent obsessive symptoms, which are most saliently related to deficits in control, are more associated with network aberrations induced during motor control.

Conclusions and Limitations

None of dACC dysfunction, deficits in motor control networks or in working memory networks are idiosyncratic to OCD. Indeed, dACC dysfunction appears to be a feature of conditions related to disordered cognitive control (Holroyd and Umemoto, 2016), across the axial diagnostic system. These effects have been documented in conditions such as schizophrenia and psychosis (Baajour et al., 2020; Woodcock et al., 2016) as well as personality disorders like borderline personality disorder (Soloff et al., 2015). Similarly, motor dysfunction is observed in conditions ranging from ADHD (Bush, 2011), autism (Lukito et al., 2020), mood disorders (Walther et al., 2012), and schizophrenia and psychosis (Abboud et al., 2017; Walther and Strik, 2012). Finally, working memory deficits are a shared characteristic across multiple diagnostic categories (Quraishi and Frangou, 2002;

Tan et al., 2007). With these considerations in mind, and given that our study lacked a clinical control group, it is obvious that we can make no generalizable assertions from our results. More generally, the question of what is specific and what is shared *across* the biological substrates of psychiatric conditions remains for now a highly vexing question. The complexity of any definitive answers is only amplified by extant genetic (Cross-Disorder Group of the Psychiatric Genomics et al., 2013) and imaging studies (Sprooten et al., 2017). What we can suggest is that within the context of OCD, using the dACC to target *in vivo* properties of motor networks appears to be a more efficient strategy for identifying clinically relevant dysfunction, than targeting working memory networks. We anticipate that such competitive frameworks will be informative in other disorders as well.

Our analysis demonstrates the value of studying disease pathology through the investigation of brain network profiles. As suggested by The National Institute of Mental Health, understanding the network profiles of diseases is of particular interest to clinical neuroscience and will inform future classification schemes (Insel et al., 2010). Here, we used fMRI and PPI to model the dACC's modulatory effects and compare between groups and tasks. While our analysis aids in understanding the punitive mechanisms of OCD, it is nevertheless precluded by the fundamental limitations that come with the use of fMRI and PPI. For example, due to the use of fMRI, our analysis could not asses the specific biochemical bases of the observed effects or differentiate between the multiple contributions to the hemodynamic response (Stephan, 2004). In addition, while the use of PPI allowed us to study the dACC's modulatory influence, it also leaves us with relatively limited inferences that can be drawn from the analysis (Logothetis, 2008). Nevertheless, our analysis has demonstrated that these methods do reveal diseaserelated network dysfunction and provides a framework that can inform future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- OCD is characterized by increased dACC modulation during Motor Control and Working Memory.
- OCD symptom dimensions predict the degree of dACC dysfunction during Motor Control and Working Memory.
- In OCD, Motor Control induces greater dACC network dysfunction than does Working Memory.
- Studying disease pathology through the investigation of network profiles yields insights that cannot be assessed by simple activation based analyses.

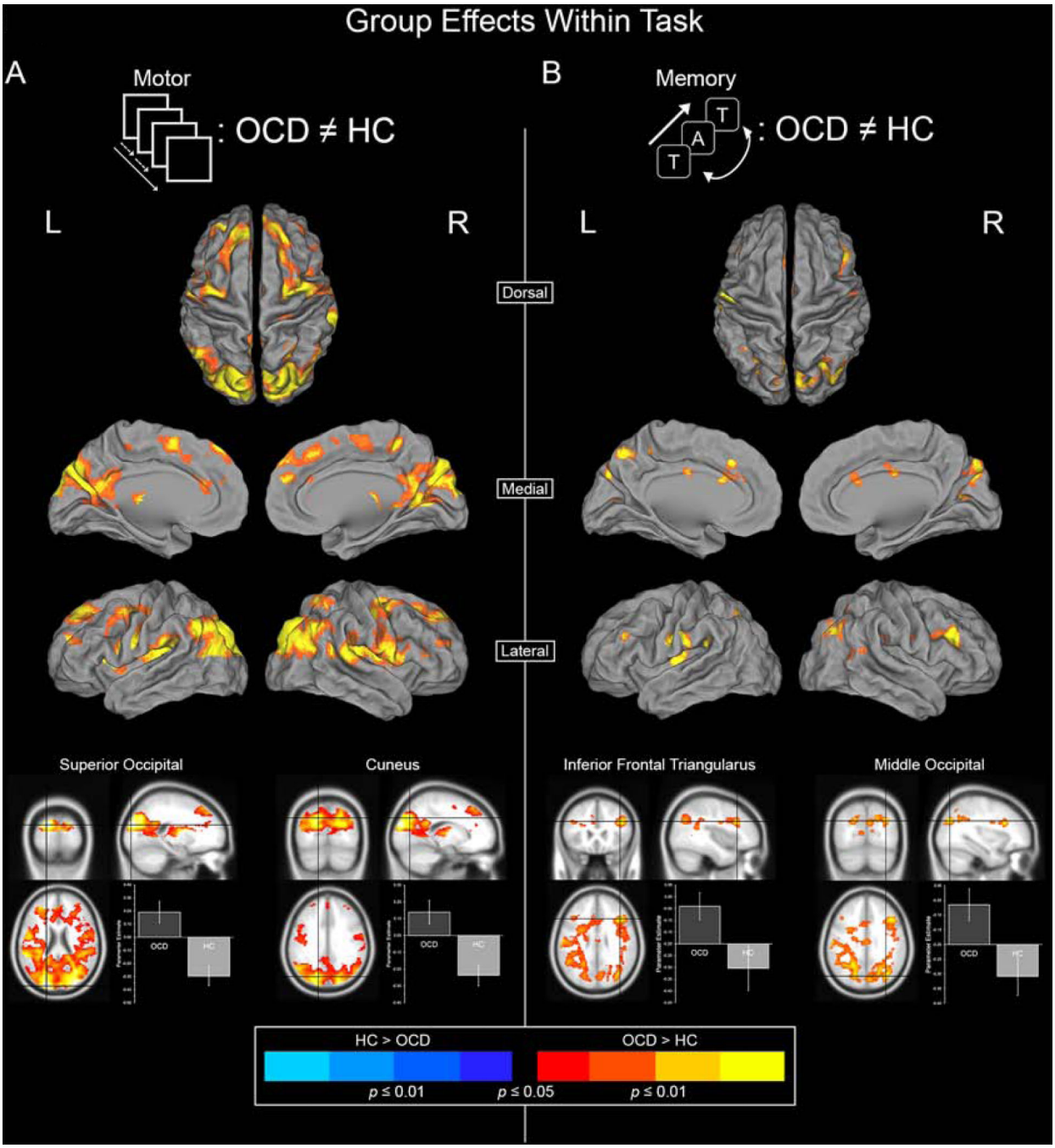

Figure 1.

Significant clusters depict areas where dACC modulation is unequal between the OCD and HC groups. Warm colors represent areas where dACC modulation is greater in OCD whereas cool colors represent areas where dACC modulation is greater in HC. (A) Inter-group differences (OCD ≠ HC) under the Motor Control task are depicted. (B) Inter-group differences under the Working Memory task are depicted. Two highly significant peaks are sampled for each task to depict the specific effects (bottom).

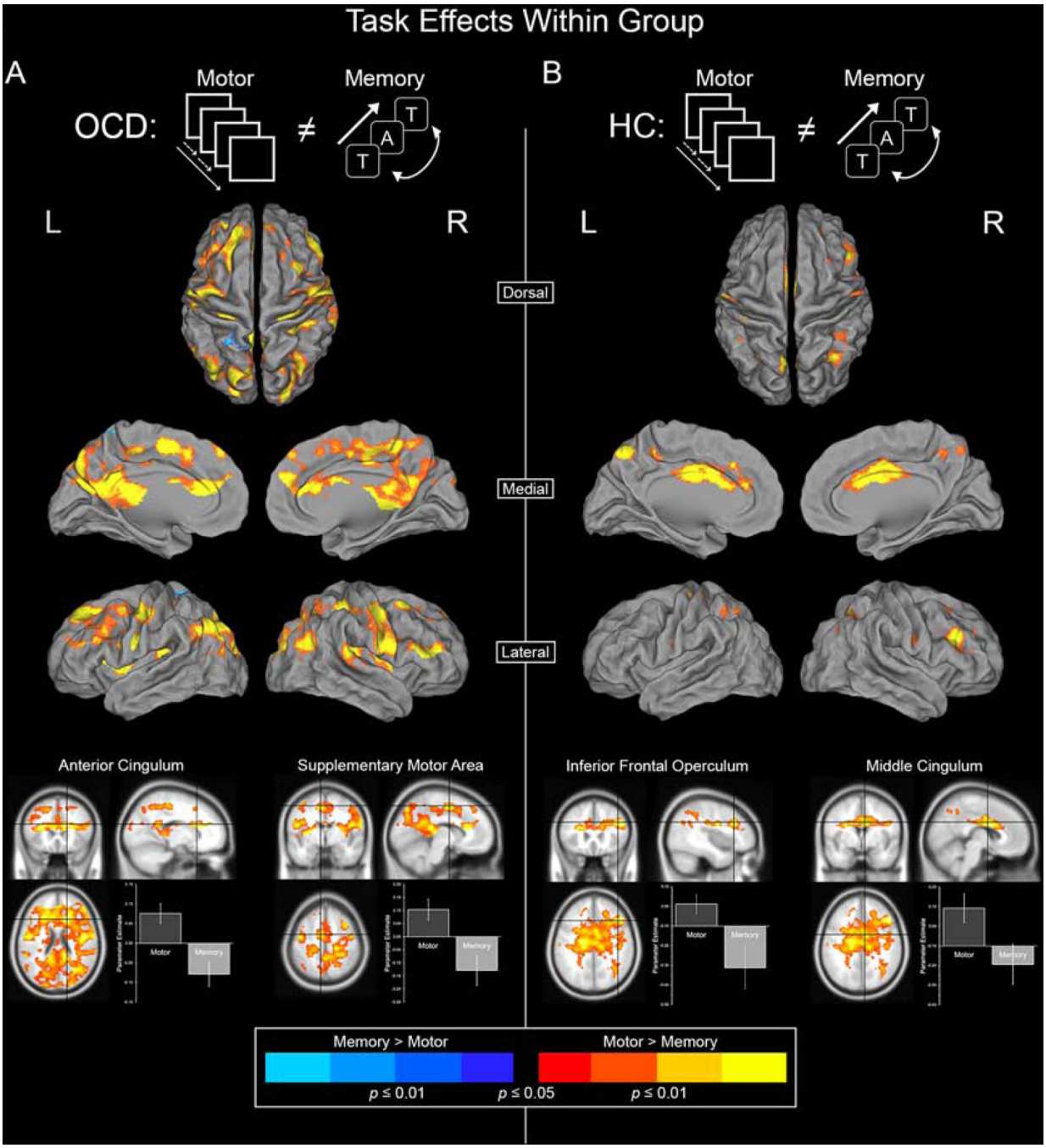

Figure 2.

Significant clusters depict areas where dACC modulation is unequal between the Motor Control and Working Memory tasks. Warm colors represent areas where dACC modulation is greater during Motor Control whereas cool colors represent areas where dACC modulation is greater during Working Memory. (A) Inter-task differences (Motor Control ≠ Working Memory) in the OCD group are depicted. (B) Inter-task differences in the HC group are depicted. Two highly significant peaks are sampled from each group to depict the specific effects (bottom).

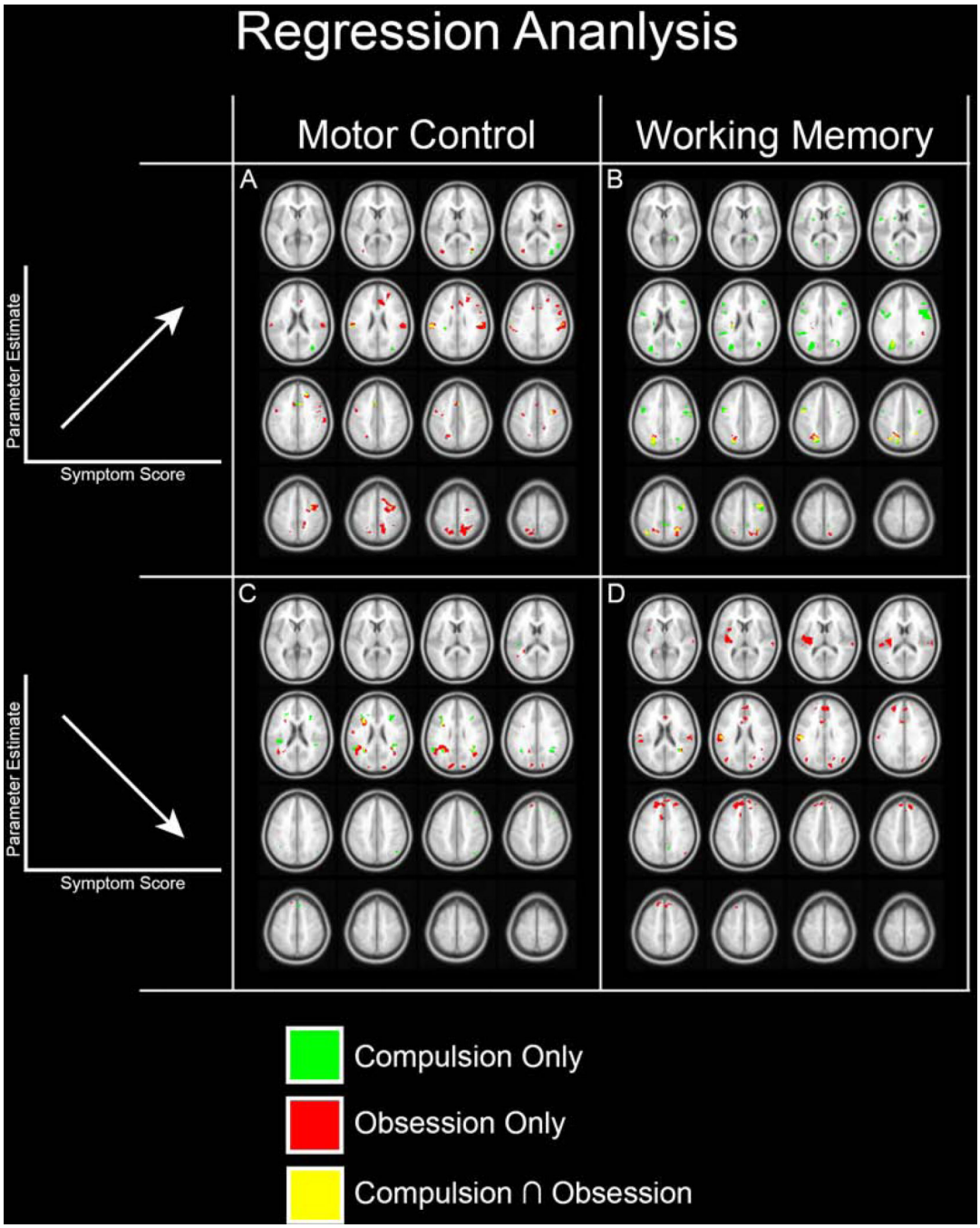

Figure 3.

We investigated whether the clusters observed in Figure 1 evinced sensitivity to symptom dimensions of OCD (based on the CY-BOCS). Accordingly, within OCD regression analyses (with Compulsions and Obsessions) were masked using the significant effects in Figure 1. Sub-clusters related to Compulsions only (green) and Obsessions only (red) are color coded. Regions where clusters overlap (Compulsions Obsessions) are separately coded (yellow). Panels A and B depict sub-clusters where the degree of dACC modulation is *positively* correlated with symptom scores (see Supplementary Animation 1). Panels C and

D depict sub-clusters where the degree of dACC modulation is negatively correlated with symptom scores (see Supplementary Animation 2).

Table 1

depicts the demographic data of our OCD and HC participants.

Group (n)	Sex (M/F)	Age (SD)	Age Range	CY-BOCS Lifetime Obsessions (SD)	CY-BOCS Lifetime Compulsions (SD)	Comorbidities	Handedness
Healthy Controls (27)	10/17	16.32 (2.70)	12.05–22.94	-	-	-	R
OCD (28)	10/18	16.53 (3.07)	12.36–21.88	13.28 (4.40)	13.25 (3.76)	None	R

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Table 2

provides information on significant clusters under the effect of group (OCD ≠ HC) during the motor control and working memory tasks. These clusters are mapped in Figure 1.

Contrast			Lobe	Automated Anatomical Labeling (AAL)	MNI Coordinates	Cluster Extent	T Score	*P* (peak)
Effect of Group	**OCD > HC**	**Motor**	**Frontal**	Frontal_Inf_Tri_L	−38 24 10	279	4.09	<0.001
				Frontal_Inf_Tri_R	34 24 12	253	2.69	0.004
				Frontal_Mid_L	−27 44 23	723	3.30	0.001
				Frontal_Mid_R	39 −7 56	633	3.06	0.001
				Frontal_Sup_L	−10 38 48	1061	2.88	0.002
				Frontal_Sup_R	36 −8 58	1377	2.94	0.002
				Frontal_Sup_Medial_L	−6 38 52	1941	3.07	0.001
			Parietal	Parietal_Sup_L	−16 −74 40	207	3.26	0.001
				Parietal_Sup_R	21 −55 53	827	3.02	0.002
				Postcentral_L	−48 −4 17	1344	3.55	<0.001
				Postcentral_R	62 −4 16	796	2.87	0.002
				Precentral_L	−48 −1 17	2348	3.45	<0.001
				Precentral_R	39 −12 46	1908	3.14	0.001
				Precunues_L	−16 −73 32	4246	3.70	<0.001
				Precunues_R	20 −74 40	112	3.00	0.002
				SupraMarginal_L	−56 −40 23	710	3.66	<0.001
				SupraMarginal_R	45 −3 22	806	3.17	0.001
				Supp_Motor_Area_L	−10 −1 54	2079	3.00	0.002
			Occipital	Occipital_Mid_L	−22 −91 20	3477	4.53	<0.001
				Occipital_Mid_R	30 −86 24	1911	4.89	<0.001
				Occipital_Sup_L	−21 −91 23	2086	4.96	<0.001
				Occipital_Sup_R	27 −88 26	2065	4.86	<0.001
				Lingual_R	2 −67 6	435	2.77	0.003
				Cuneus_L	−16 −76 34	5091	4.19	<0.001
			Temporal	Temporal_Sup_L	−54 −40 22	712	3.83	<0.001

Contrast		Lobe	Automated Anatomical Labeling (AAL)	MNI Coordinates	Cluster Extent	T Score	*P* (peak)
			Temporal_Sup_R	57 −36 14	1713	3.48	<0.001
			Insula_L	−38 10 8	1427	3.99	<0.001
			Insula_R	38 14 8	959	3.67	<0.001
		Thalamic	Thalamus_L	−12 −18 10	713	3.26	0.001
			Thalamus_R	21 −25 5	398	3.14	0.001
			-	-	-	-	-
	Memory	**Frontal**	Frontal_Inf_Tri_L	−40 24 26	154	2.15	0.017
			Frontal_Inf_Tri_R	40 23 28	586	3.03	0.002
			Frontal_Sup_R	18 16 58	100	2.37	0.010
		Parietal	Parietal_lnf_R	48 −52 46	180	2.11	0.019
			Parietal_Sup_L	−18−46 64	225	2.69	0.004
			Parietal_Sup_R	32 −50 59	155	2.11	0.019
			Postcentral_L	−58−13 23	654	2.69	0.004
			Postcentral_R	51 −13 28	125	1.90	0.029
			Precunues_L	−18−62 34	841	2.77	0.003
			Precunues_R	16−52 40	510	2.40	0.009
			SupraMarginal_L	−48 −49 28	675	2.51	0.007
		Temporal	Temporal_Sup_R	63 −25 4	525	2.43	0.008
			lnsula_L	−39−16 6	296	2.33	0.011
			-	-	-	-	-
		Occipital	Occipital_Mid_L	−20 −60 35	213	2.64	0.005
			Occipital_Mid_R	34 −74 30	672	3.02	0.002
			Occipital_Sup_L	−20 −68 32	580	2.68	0.004
			Occipital_Sup_R	24 −62 34	590	2.66	0.004
			Calcarine_L	−20 −54 4	123	2.28	0.012
			Calcarine_R	24−49 4	199	2.26	0.013
			Cuneus_L	−18−72 34	328	2.51	0.006
			Cuneus_R	20 −70 34	1050	2.46	0.007

Contrast		Lobe	Automated Anatomical Labeling (AAL)	MNI Coordinates	Cluster Extent	T Score	*P* (peak)
HC > OCD	Motor	Parietal	Precentral_L	−39 −28 64	42	2.91	0.002
			-	-	-	-	-
			-	-	-	-	
			-	-	-	-	-
	Memory	None	-	-	-	-	-
			-	-	-	-	-

Table 3

provides information on significant clusters under the effect of task (Motor Control ≠ Working Memory) in the OCD and HC groups. These clusters are mapped in Figure 2.

Contrast			Lobe	Automated Anatomical Labeling (AAL)	MNI Coordinates	Cluster Extent	T Score	*P* (peak)
Effect of Task	**Motor > Memory**	**OCD**	**Frontal**	Frontal_Sup_L	−18 34 48	1007	3.03	0.002
				Frontal_Inf_Tri_L	−32 23 14	752	3.43	<0.001
				Frontal_Inf_Tri_R	50 29 12	1000	3.28	0.001
				Frontal_Mid_L	−28 38 16	608	2.87	0.002
				Frontal_Mid_R	45 41 22	713	3.02	0.002
				Frotal_Sup_R	26 32 50	378	2.48	0.007
			Parietal	Parietal_Inf_L	−28 −79 41	250	2.76	0.003
				Parietal_Inf_R	32−40 52	228	2.70	0.004
				Postcentral_L	−50 −7 20	1764	3.18	0.001
				Postcentral_R	62 −8 23	2067	2.90	0.002
				Precentral_L	−46 −7 20	2338	3.21	0.001
				Precentral_R	40 −13 47	2194	3.40	<0.001
				Precuneus_L	−8 −79 48	5243	2.90	0.002
				Supp_Motor_Area_L	−8 −4 53	2818	3.22	0.001
				Angular_L	−50 −67 34	1162	2.61	0.005
				Angular_R	39 −61 23	1218	2.87	0.002
			Temporal	Temporal_Sup_L	−56 −38 18	309	2.68	0.004
				Temporal_Sup_R	52 −37 18	1258	2.56	0.006
				Cingulum_Ant_R	10 22 22	2232	3.38	0.001
				Cingulum_Mid_L	−6 −6 50	3427	3.15	0.001
				Cingulum_Post_R	10 −40 20	1666	3.07	0.001
			Occipital	Occipital_Mid_L	−27 −79 38	1692	2.96	0.002
				Occipital_Mid_R	32 −66 26	1142	2.91	0.002
				Occipital_Sup_L	−27 −76 40	1162	2.76	0.003
				Occipital_Sup_R	34 −74 44	1417	2.91	0.002

Contrast		Lobe	Automated Anatomical Labeling (AAL)	MNI Coordinates	Cluster Extent	T Score	*P* (peak)
Memory > Motor	HC	Frontal	Calcarine_L	−24 −66 12	500	2.35	0.010
			Calcarine_R	22 −54 17	91	2.45	0.008
			Frontal_Mid_L	−48 23 32	125	2.67	0.004
			Frontal_Mid_R	46 24 32	717	3.05	0.001
			Frontal_Sup_L	−16 38 29	132	2.19	0.015
			Frontal_Sup_R	21 34 28	247	2.64	0.005
		Pareietal	Parietal_Inf_L	−40 −50 47	344	2.03	0.022
			Parietal_Inf_R	39 −56 48	347	2.03	0.013
			Postcentral_L	−45 −20 29	297	2.39	0.008
			Postcentral_R	45 −20 32	266	2.28	0.012
			Precentral_L	−32 −26 64	202	2.28	0.012
			Precentral_R	48 −2 28	160	2.42	0.009
			Precuneus_L	−8 −67 28	1362	3.04	0.001
			Angular_R	33 −62 48	800	2.53	0.006
			Caudate_L	−16 6 24	192	2.87	0.002
		Temporal	Temporal_Sup_R	60 −22 2	365	2.86	0.003
			Cingulum_Ant_R	6 5 28	1148	2.90	0.002
			Cingulum_Mid_R	6 0 29	2422	2.77	0.003
	OCD	Parietal	Parietal_Sup_L	−18 −46 64	92	2.77	0.003
			-	-	-	-	-
			-	-	-	-	-
	HC	-	-	-	-	-	-

Table 4

provides information on clusters under the effect of group where dACC modulation is predicted by lifetime obsessive or lifetime compulsive symptom dimensions. These clusters are represented in Figure 3.

Compulsion / Working Memory									
Positive					**Negative**				
AAL	**MNI Coordinates**	**Cluster Extent**	**T Score**	***P* (peak)**	**AAL**	**MNI Coordinates**	**Cluster Extent**	**T Score**	***P* (peak)**
Precentral_L	−50 −1 41	826	3.77	<0.001	Postcentral_L	−52 −20 26	177	2.68	0.006
Occipital_Sup_L	−24 −73 32	1650	3.70	0.001	Temporal_Mid_R	33 −52 20	65	2.23	0.017
Postcentral_R	58 −2 34	689	3.35	0.001	Precuneus_R	14 −54 38	54	2.16	0.020
Precentral_R	42 −1 48	488	3.10	0.002	-	-	-	-	-
Frontal_Inf_Tri_R	48 29 24	402	2.78	0.005	-	-	-	-	-
Occipital_Mid_R	34 −67 23	312	2.72	0.006	-	-	-	-	-
SupraMarginal_L	−62 −43 29	201	2.63	0.007	-	-	-	-	-
Caudate_L	−24 −26 24	116	2.56	0.008	-	-	-	-	-
Frontal_Inf_Tri_L	−48 28 28	58	2.55	0.008	-	-	-	-	-
Parietal_Inf_R	30 −52 52	159	2.54	0.009	-	-	-	-	-
Calcarine_R	9 −90 11	58	2.43	0.011	-	-	-	-	-
Putamen_R	28 8 12	50	2.40	0.012	-	-	-	-	-
Cingulum_Mid_L	0 −40 54	124	2.26	0.016	-	-	-	-	-
Calcarine_R	18 −48 6	50	2.23	0.017	-	-	-	-	-
Putamen_L	−24 −2 12	75	2.22	0.017	-	-	-	-	-
Frontal_Inf_Oper_R	45 10 14	78	2.17	0.019	-	-	-	-	-
Precuneus_R	15 −66 34	102	2.17	0.019	-	-	-	-	-
Calcarine_L	−20 −58 14	87	2.17	0.019	-	-	-	-	-
Obsession / Working Memory									
Positive					**Negative**				
AAL	**MNI Coordinates**	**Cluster Extent**	**T Score**	***P* (peak)**	**AAL**	**MNI Coordinates**	**Cluster Extent**	**T Score**	***P* (peak)**
Precuneus_L	−14 −60 50	1113	3.80	<0.001	Occipital_Mid_R	44 −76 29	195	3.49	0.001
Frontal_Mid_R	46 2 52	192	3.17	0.002	Insula_L	−34 −19 11	1552	3.48	0.001

Compulsion / Working Memory

Positive					Negative				
AAL	**MNI Coordinates**	**Cluster Extent**	**T Score**	***P* (peak)**	**AAL**	**MNI Coordinates**	**Cluster Extent**	**T Score**	***P* (peak)**
Parietal_Inf_R	30 −52 52	454	3.08	0.002	Frontal_Sup_Medial_L	−6 42 48	1614	2.95	0.003
Precentral_L	−45 −2 42	92	2.77	0.005	Temporal_Sup_R	66 −25 16	285	2.62	0.007
Insula_L	−24 −30 26	65	2.70	0.006	Cingulum_Ant_L	−8 11 28	416	2.40	0.012
-	-	-	-	-	Occipital_Mid_L	−40 −73 26	143	2.26	0.016
-	-	-	-	-	Cuneus_R	15 −86 26	139	2.25	0.017
-	-	-	-	-	Insula_L	−34 5 8	115	2.24	0.017
-	-	-	-	-	Angular_R	38−48 22	78	2.20	0.018
-	-	-	-	-	Cuneus_R	22 −70 26	64	2.04	0.025

Compulsion / Motor Control

Positive					Negative				
AAL	**MNI Coordinates**	**Cluster Extent**	**T Score**	**P (peak)**	**AAL**	**MNI Coordinates**	**Cluster Extent**	**T Score**	***P* (peak)**
Precentral_R	33 −4 44	127	2.91	0.004	Frontal_Mid_R	42 23 47	66	3.08	0.002
Cingulum_Mid_R	4 16 40	169	2.90	0.004	SupraMarginal_R	44 −38 23	394	2.61	0.007
Frontal_Sup_R	20 36 35	50	2.76	0.005	Rolandic_Oper_L	−40 −31 20	181	2.60	0.008
SupraMarginal_L	−56 −25 26	149	2.47	0.010	Frontal_Inf_Oper_L	−28 14 26	318	2.59	0.008
SupraMarginal_R	54 −24 30	73	2.46	0.010	SupraMarginal_L	−54 −48 24	168	2.47	0.010
Temporal_Mid_R	50 −60 16	118	2.34	0.014	Frontal_Inf_Tri_R	32 22 23	250	2.43	0.011
Occipital_Mid_R	30 −76	328	2.10	0.023	Angular_L	−30 −54 28	201	2.40	0.012
-	-	-	-	-	Frontal_Sup_Medial_R	4 32 53	75	2.28	0.015
-	-	-	-	-	Angular_R	46 −64 38	96	2.02	0.026

Obsession / Motor Control

Positive					Negative				
AAL	**MNI Coordinates**	**Cluster Extent**	**T Score**	***P* (peak)**	**AAL**	**MNI Coordinates**	**Cluster Extent**	**T Score**	***P* (peak)**
Postcentral_R	57 −22 34	981	4.02	<0.001	Frontal_Inf_Oper_L	−28 10 26	306	3.84	<0.001
Frontal_Mid_R	38 −2 52	820	3.67	0.001	Angular_L	−36 −44 26	889	2.97	0.003

Compulsion / Working Memory									
Positive					Negative				
AAL	MNI Coordinates	Cluster Extent	T Score	*P* (peak)	AAL	MNI Coordinates	Cluster Extent	T Score	*P* (peak)
SupraMarginal_L	−60 −24 24	361	3.62	0.001	Occipital_Sup_R	18 −91 28	144	2.47	0.010
Cingulum_Mid_R	8 12 35	347	3.45	0.001	Cuneus	−10 −85 30	164	2.45	0.011
Postcentral_R	12 −43 60	762	3.43	0.001	Angular_R	40 −61 26	259	2.44	0.011
Parietal_Sup_L	−26 −52 64	458	3.35	0.001	-	-	-	-	-
Frontal_Sup_R	20 36 35	319	3.24	0.002	-	-	-	-	
Precentral_L	−33 −10 44	58	3.17	0.002	-	-	-	-	-
Precentral_L	−50 −2 42	124	3.08	0.002	-	-	-	-	-
Cingulum_Ant_R	9 28 24	257	3.07	0.002	-	-	-	-	-
Precentral_R	52 5 34	131	2.53	0.009	-	-	-	-	-
Occipial_Mid_L	−32 −73 12	161	2.51	0.009	-	-	-	-	-
Frontal_Inf_Oper_R	45 20 30	116	2.38	0.012	-	-	-	-	-