Published in final edited form as:

Curr Opin Neurol. 2012 August ; 25(4): 392–401. doi:10.1097/WCO.0b013e328355aa94.

Functional brain networks in movement disorders: recent advances

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Abstract

Purpose of review—Different neuroimaging techniques have been used to identify disease-specific functional brain networks in Parkinson's disease, atypical parkinsonian syndromes, and other movement disorders. This review highlights recent advances in network imaging and its clinical applications in movement disorders.

Recent findings—Positron emission tomography and functional MRI studies have revealed distinct, abnormal metabolic brain networks and altered interregional connectivity in Parkinson's disease and related movement disorders. Network-level functional changes have been found to correlate with disease severity and progression. Moreover, network-based categorization algorithms are proving useful in enhancing the accuracy of clinical diagnosis in patients with early symptoms and in providing objective evidence of treatment response.

Summary—Although in most movement disorders the predominant histopathology involves the basal ganglia, including the substantia nigra, functional changes in relevant neural circuits are not limited to these structures. The current advances in functional brain imaging have contributed to a better pathophysiological understanding of movement disorders as complex alterations of widespread functional brain networks. The promising findings from recent studies may help to establish new and reliable biomarkers to monitor disease progression and treatment effects in future clinical trials.

Keywords

brain networks; dystonia; functional connectivity; Huntington's disease; neuroimaging; Parkinson's disease; Tourette syndrome

INTRODUCTION

In this review, we summarize recent advances in the use of functional brain imaging to study Parkinson's disease and other movement disorders. Spatial covariance analysis has been particularly useful in delineating abnormal metabolic networks associated with these diseases. Moreover, this approach has allowed the quantification of network activity at the

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Conflicts of interest

There are no conflicts of interest.

individual subject level. Indeed, these measurements have been used for differential diagnosis, as well as the objective assessment of disease progression and the response to therapies for these diseases. The computational details underlying this method have been provided elsewhere [1–3]. In addition to advances in this area, substantial progress has been made in using measures of anatomical and functional connectivity to study disease-related changes within specific circuits. The details of these approaches and their applications in the study of brain disease have been the topic of several recent reviews (e.g. [4–6]).

PARKINSON'S DISEASE AND RELATED DISORDERS

The diagnosis of Parkinson's disease is made clinically based upon its cardinal motor symptoms of rigidity, bradykinesia, resting tremor, and postural instability. In addition to the motor symptoms, executive and memory dysfunction, and deterioration of visuospatial processing are encountered frequently in Parkinson's disease patients, even at early clinical stages of the disease [7]. Using different analytical methods, several groups have identified distinct patterns of resting metabolic activity and abnormal functional connectivity associated with the motor and cognitive manifestations of the disorder.

Motor circuits

Resting state metabolic brain imaging using ^{18}F -fluorodeoxyglucose (FDG) and PET reveals the consistent presence of an abnormal disease-related network relating to motor manifestations [1,8]. This Parkinson's disease-related spatial covariance pattern (PDRP) is characterized by increased metabolic activity in the putamen/globus pallidus, thalamus, pons, cerebellum, and sensorimotor cortex, accompanied by relative reductions in the premotor cortex (PMC) and parietal association cortex. The biological interpretation of the regional changes that comprise this network, particularly the meaning of the relative hypermetabolism seen in the regions with positive loadings, has been discussed elsewhere [3,9,10]. The observed spatial topography conforms closely to changes in local synaptic activity inferred from experimental models of the disease [11]. Indeed, this point is highlighted by the recent demonstration of a homologous metabolic pattern in a nonhuman primate model of parkinsonism [12]. Moreover, the PDRP topography has been replicated in multiple patient populations, scanned using a variety of imaging methods [1].

In addition, subject scores quantifying pattern expression in individual patients have been found to exhibit a high degree of stability on repeated measurement over days to weeks [13], a prerequisite for applying this measure as a reliable imaging descriptor of disease progression. Indeed, PDRP expression was found to progress linearly over time in early-stage patients [14]. In a recent follow-up study, Tang *et al.* [10] examined network progression on a hemisphere by hemisphere basis, and found that 'presymptomatic' values (measured in cerebral hemispheres ipsilateral to affected limbs in patients with hemiparkinsonism) were already abnormally elevated approximately 2 years prior to symptom onset. This suggests that elevated network activity in Parkinson's disease patients is not simply a manifestation of concurrent motor symptoms. Rather, PDRP expression likely relates to systems-level alterations in the function of cortico-striato-pallido-thalamo-cortical (CSPTC) motor pathways as suggested by correlations with intraoperative recordings of cell activity in the subthalamic nucleus (STN), a key modulator of basal

ganglia output [15]. Indeed, as with PDRP activity, STN firing rates were found to be elevated before the appearance of motor signs in experimental disease models [16].

Parallel research efforts have helped to elucidate the changes in functional connectivity that underlie the PDRP network topography. Functional MRI (fMRI) methods have been increasingly used to measure resting state blood oxygen level-dependent (BOLD) signal and changes in functional connectivity in Parkinson's disease and other brain disorders (see [5] for methodological review). A study of the effect of dopamine on different striato-cortical motor loops [17] revealed that in Parkinson's disease, functional connectivity was decreased in pathways linking the more severely dopamine-depleted posterior putamen with sensorimotor and inferior parietal cortex. By contrast, an increase in functional connectivity relative to healthy individuals was evident in pathways between the less dopamine-depleted anterior putamen and the cortical areas. The authors suggested that the gradient of attrition of nigrostriatal dopaminergic terminals is manifested functionally by differences in the activity of CSPTC motor circuits with concomitant effects on task performance. On the other hand, there is increasing evidence that dopamine depletion of the basal ganglia may actually lead to increased functional connectivity (hypersynchronization) within the striatocortical pathways that may be involved in the generation of motor symptoms in Parkinson's disease [18,19]. It is perhaps noteworthy that most of the functional connectivity changes observed in Parkinson's disease patients undergoing resting-state (rs)-fMRI were localized to projections linking the various PDRP nodes (e.g. [20,21]). A recent arterial spin labeling (ASL) MRI resting-state perfusion study in Parkinson's disease is relevant in this regard [22]. These investigators employed the same algorithm that had been previously applied to FDG PET data to identify a significant disease-related spatial covariance pattern characterized by decreased perfusion in the prefrontal and parieto-occipital regions associated with relative increases (positive region weights) in the putamen, globus pallidus, sensorimotor cortex, supplementary motor area (SMA), and anterior cingulate cortex (ACC). Pattern expression in individual patients correlated with United Parkinson's Disease Rating Scale (UPDRS) motor ratings and behavioral measures, consistent with the observed topographic homology with the PDRP motor network as well as the Parkinson's disease cognition-related metabolic pattern (see below). This study, and the earlier demonstration of comparable PDRP values measured in ASL MRI and FDG PET scans from the same patients [23] point to the promise of advanced magnetic resonance techniques in the evaluation of movement disorders and other brain diseases at the systems level.

Several studies have investigated changes in effective connectivity in Parkinson's disease patients using task-based fMRI with psychophysical interaction (PPI) analysis (e.g. [24,25]). Wu *et al.* [24] studied patients and control individuals executing self-initiated movements and found decreased connectivity in pathways connecting the putamen with the PMC and the SMA, as well as those linking the putamen and the cerebellum. By contrast, during movement initiation, connectivity between cortical motor regions and the cerebellum increased in Parkinson's disease relative to healthy control individuals [24]. Interestingly, UPDRS motor ratings in the patients correlated with connectivity in the latter pathways, suggesting that they serve a compensatory role in task performance [24–27].

Reductions in task-related responses in the pre-SMA and SMA – regions essential for the planning and initiation of movement – have been consistently reported in motor activation studies performed in Parkinson’s disease patients [25] (cf. [28,29]). This change has been attributed to a deficiency in cortical facilitation through CSPTC pathways during self-initiated movements [25,30]. Concurrent increases in connectivity in pathways involving cerebellum, PMC, parietal and prefrontal regions may compensate for the functional decline in the motor circuits seen with advancing disease [25,31,32].

That said, group differences in the baseline condition may have bearing on the interpretation of these observations. Recent PET measurements of glucose utilization and regional cerebral blood flow (rCBF) in Parkinson's disease patients point to the presence of abnormal elevations in resting synaptic activity in the SMA as well as other regions (e.g. [10,33]). In Parkinson's disease, this may be attributed to hypersynchronization and 'hyper direct' projections of the PMC and SMA to the STN [34]. Indeed, Baudrexel *et al.* [35] recently reported increased functional connectivity between the STN and the sensorimotor cortex (including SMA) in Parkinson's disease patients. It remains unclear, however, whether reduced SMA activation during movement in Parkinson's disease patients is indicative of a 'ceiling effect' imposed by the abnormally high baseline activity that is present at early disease stages [10,14].

In this vein, recent evidence supports the notion that tremor is mediated by different functional circuits than those subserving akinesia and rigidity. Several fMRI studies implicate changes in the cerebello-thalamo-cortical (CbTC) pathways – and altered functional connectivity in basal ganglia projections to these circuits – in the pathogenesis of Parkinson’s disease tremor [36,37,38^{***}]. Along these lines, Mure *et al.* [39^{*}] recently identified a Parkinson’s disease tremor-related spatial covariance pattern (PDTP) that is distinct from the PDRP. This metabolic network was identified using a within-patient network analysis [40] of scans from tremor-dominant Parkinson’s disease patients acquired on and off-stimulation of the ventro intermedial thalamic (Vim) nucleus [39^{*}]. The PDTP is characterized by covarying increases in cerebellar (dentate nucleus), motor cortical, and basal ganglia metabolic activity that were reduced by stimulation. In the baseline condition, PDTP expression correlated with UPDRS tremor ratings but not with akinesia/rigidity, whereas in the same patients PDRP expression correlated with akinesia/rigidity and not with tremor ratings. Indeed, in accord with the clinical findings, Vim thalamic stimulation was associated with significant changes in PDTP but not PDRP activity [39^{*}].

Effects of treatment

In general, dopamine replacement for Parkinson's disease motor symptoms and STN deep brain stimulation (DBS) both are associated with significant reduction in PDRP expression, which correlates with individual differences in the clinical response to treatment [41,42^{''}]. In keeping with these observations, correction of functional connectivity changes with dopaminergic treatment has been a consistent finding in task-based and rs-fMRI studies (e.g. [43,44]). For instance, Palmer *et al.* [45] described treatment-mediated increases in functional connectivity in pathways linking the ACC and the caudate and putamen. Moreover, levodopa treatment was associated with reductions in effective connectivity in

pathways between the output nuclei of the basal ganglia and cortical motor regions [45], and also with improvement in the efficacy of these networks as determined by measurements of 'small world-ness' using graph theoretic formulations [44].

These approaches have also led to new insights into the mechanisms of treatment side-effects, most notably levodopa-induced dyskinesia (LID). In untreated patients, PDRP expression is tightly coupled in scans of cerebral metabolism and perfusion [46,47]. Nonetheless, levodopa infusion led to a consistent dissociation between metabolic (synaptic) and hemodynamic (microvascular) responses at both regional and network levels [47]. Interestingly, this phenomenon, termed flow–metabolism dissociation (FMD), was seen only with dopaminergic treatment and was not evident during STN stimulation with comparable improvement in motor ratings. Moreover, the magnitude of FMD measured during levodopa infusion was substantially greater in Parkinson's disease patients exhibiting dyskinesias during treatment. Further analysis revealed that increased FMD in LID patients was attributable to hemodynamic rather than synaptic effects, supporting the possibility of underlying angiogenesis and permeability changes in the pathogenesis of this common side-effect of dopaminergic pharmacotherapy [48]. Indeed, dissociation between local metabolic activity and rCBF in homologous brain areas has recently been reported by autoradiography in a rat model of LID [49]. The recent description of an association between LID and increased vascular endothelial growth factor (VEGF) expression [50] in the rat and in post-mortem samples from Parkinson's disease patients provides additional support for this intriguing hypothesis.

Cognitive circuits

In addition to motor disability, cognitive dysfunction occurs in the majority of Parkinson's disease patients and has a substantial impact on quality of life [51]. Utilizing spatial covariance analysis, Huang *et al.* [52] identified and validated a topographically distinct metabolic brain network associated with the cognitive manifestations of the disorder (cf. [1,53]). This Parkinson's disease-related cognitive pattern (PDCP) is characterized by metabolic reductions in the pre-SMA, prefrontal cortex, precuneus, and parietal association cortex, covarying with relatively increased activity in the cerebellar vermis and the dentate nuclei. In contrast to the PDRP, PDCP expression at the group level was not altered during the treatment of Parkinson's disease motor symptoms with either dopaminergic pharmacotherapy or DBS [52]. Moreover, the hemodynamic effects of levodopa on PDRP activity (see above) were not evident in PDCP regions [47]. That said, recent evidence suggests that treatment-mediated changes in PDCP activity – and concurrent measures of cognitive performance – can be discerned at the individual subject level based upon the degree of expression present at baseline [42²²]. Of note, Parkinson's disease patients with low (i.e. more normal) baseline PDCP activity exhibited reductions in cognitive performance during levodopa treatment, consistent with potential overdose effects [54]. Indeed, patient differences in the integrity of nigral dopaminergic projections to the caudate nucleus and genetic factors such as catechol-O-methyltransferase polymorphisms may influence baseline PDCP expression and the cognitive response to dopaminergic medication [55–58].

The mechanisms underlying the effects of DBS on cognitive functioning in Parkinson's disease patients are less well understood. Indeed, a recent review of this topic suggests that STN DBS improves certain aspects of cognitive function but may worsen others [59]. A recent imaging study used a network approach to compare changes in sequence learning performance and associated activation responses during STN stimulation with analogous measures acquired in the same patients during a levodopa infusion that was titrated to achieve an equivalent motor response [33^{***}]. Improved sequence learning during stimulation involved the deployment of a specific lateral cerebellar–premotor network during task performance (Fig. 1a and b), which was not potentiated by levodopa treatment. Nodal analysis revealed that the two interventions differed most in the SMA, in which baseline overactivity was normalized consistently by stimulation and not levodopa (Fig. 1c). The beneficial effects of STN DBS were attributed to direct modulation of SMA–STN projections during both simple movement and more complex functions, such as sequence learning.

Functional brain networks in the differential diagnosis of parkinsonian syndromes

The use of imaging techniques to enhance the accuracy of differential diagnosis in movement disorders has been studied extensively [60–62]. Because of their speed and objectivity, computerized image-based classification algorithms have generated considerable interest in this regard. Such approaches may be particularly valuable at early disease stages, when conclusive diagnostic signs have yet to manifest clinically. Tang *et al.* [63] used the PDRP and previously validated spatial covariance patterns for multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) in an automated logistical algorithm to discriminate Parkinson's disease from these two most common atypical parkinsonian syndromes misdiagnosed as this condition in tertiary referral centers. The distinctive metabolic features of the MSA and PSP-related patterns (MSARP and PSPRP) have been discussed elsewhere [64–66]. The authors computed subject scores for the three patterns in FDG PET scans from 167 patients with clinically indeterminate parkinsonism. Comparison with the ultimate clinical diagnosis (the 'gold standard') revealed that the pattern-based classifications were highly accurate, agreeing well with clinical diagnoses reached on average 2.6 years after imaging. Despite rigorous cross-validation, the ultimate utility of this approach will be known only following the completion of prospective diagnostic studies that are currently ongoing.

HYPERKINETIC MOVEMENT DISORDERS

Alongside the comprehensive studies investigating functional brain networks in parkinsonian syndromes, similar imaging techniques have been utilized to study abnormal brain networks in hyper-kinetic movement disorders.

Huntington's disease

Huntington's disease is an autosomal dominant inherited disease caused by expansion of a CAG repeat in the huntingtin gene. The genetic predictability of this neurodegenerative disease makes it unique in that structural and functional alterations of the brain can be investigated years before clinical onset.

Wolf *et al.* [67^{*}] utilized continuous ASL MRI and independent component analysis to identify patterns of abnormal resting state rCBF in presymptomatic Huntington's disease mutation carriers. They reported reduced activity of a fronto-striatal network involving the dorsolateral prefrontal cortex (DLPFC), particularly in patients approaching phenoconversion. Increased activity was found in the left precuneus, possibly compensatory in nature [67^{*}]. Indeed, there is emerging evidence that regional increases in metabolic and hemodynamic cortical activity might compensate for the progressive decline evident in the basal ganglia [68,69]. Functional decline in prefrontal brain circuits has also been linked to cognitive performance in presymptomatic Huntington's disease [70].

Recently, the effects of external globus pallidus (GPe) DBS on regional brain function have been investigated in symptomatic Huntington's disease patients [71^{*}]. In the resting state, rCBF was reduced in the globus pallidus, putamen, thalamus and SMA, sensorimotor cortex and prefrontal cortex, whereas rCBF in the cerebellum was relatively increased above normal levels. GPe stimulation improved connectivity within CSPTC pathways but did not alter the cerebellar abnormalities that were evident at baseline. This finding is in line with an earlier study of presymptomatic increases in resting cerebellar activity, which continue after phenoconversion [68].

Primary torsion dystonia

Primary torsion dystonia (PTD) is a hyperkinetic movement disorder characterized by involuntary and sustained muscle contraction [72]. Many forms of PTD have genetic causes. The two most common mutations have been localized in the *DYT1* and *DYT6* genes, with variable clinical penetrance. PTD is commonly attributed to basal ganglia dysfunction and impaired sensorimotor integration, although the specific histopathological correlates are still unknown [73]. More recently, evidence emerged showing that the cerebellum may also be involved in the pathophysiology of PTD (e.g. [74,75]). Argyelan *et al.* [76] used diffusion tensor imaging (DTI) and probabilistic tractography to identify reduced structural connectivity in tracts linking the cerebellum to the ventral thalamus in both manifesting and nonmanifesting dystonia mutation carriers. Interestingly, nonmanifesting gene carriers were distinguished by the presence of an additional distal tract abnormality involving the pathway segment linking the thalamus to the motor cortex. This finding suggests that a second 'protective' abnormality regulates clinical penetrance in dystonia gene carriers. Thus, abnormal cerebello-thalamic outflow is thought to cause aberrant facilitation of sensorimotor cortical inhibition only when the distal segment of the CbTC pathway is relatively intact. Along these lines, a recent study in an experimental knock-in mouse model revealed decreased integrity of the CbTC pathways involving both segments, which is consistent with the nonpenetrant states of these animals [77^{*}].

Tourette syndrome

Tourette syndrome is a neurodevelopmental disorder characterized by involuntary, repetitive movements and vocalizations termed tics. The clinical presentation of Tourette syndrome is heterogeneous and Tourette syndrome is commonly accompanied by other behavioral disorders such as obsessive compulsive disorder (OCD) and attention deficit hyperactivity syndrome (ADHD) [78]. Although the pathophysiology of Tourette syndrome remains

unclear, increasing evidence suggests that abnormalities within different CSPTC circuits and deterioration of adaptive motor control underlie the heterogeneous clinical presentation of the syndrome [78–81,82[■]]. Recent rs-fMRI findings suggest that these alterations might be caused by developmental immaturity of the neuronal pathways linking the major nodes of these networks [79,82[■]]. Increased activity, predominantly in frontal and parietal regions, cingulate cortex, and caudate nucleus, might compensate for the functional decline in CSPTC and fronto-parietal circuits during voluntary movement [81,83]. Alternatively, it has been suggested that elevated activity in these regions as compared to healthy controls might rather display a failure to deactivate and thus reflect an immediate neural correlate of the motor manifestations of the disease [83]. Of note, distinct functional networks associated with specific symptoms of Tourette syndrome have recently been identified [82[■],84[■]]. Spatial covariance analysis of metabolic imaging data from patients with Tourette syndrome revealed a disease-related pattern (TSRP) characterized by decreased activity in the striatum and orbitofrontal cortex with relative increases in the PMC and cerebellum (Fig. 2a) [84[■]]. Whereas TSRP scores reliably separated Tourette syndrome patients from healthy control individuals (Fig. 2b), pattern expression did not correlate with measures of clinical severity. Interestingly, a separate metabolic pattern was identified that correlated with the presence of OCD symptoms. This pattern was independent of the TSRP, and was characterized by reduced ACC and DLPFC activity and by relative increases in the PMC and precuneus (Fig. 3). Similar findings were reported subsequently by Worbe *et al.* [82[■]], who found a correlation between OCD ratings and altered functional connectivity within a distinct network involving the DLPFC and orbitofrontal regions.

CONCLUSION

The advances in functional brain imaging in the past years have considerably enhanced our pathophysiological understanding of movement disorders. Although their histopathological hallmark is located in the basal ganglia, movement disorders are caused by alterations within functional whole brain networks rather than localized neurodegeneration. Distinct disruptions within neural circuits connecting the network nodes are critically involved in the manifestation of motor and non-motor symptoms. Moreover, proper function of these neural networks is closely related to the integrity of the dopaminergic system. Functional changes within the networks occur early, even in premanifest disease stages. Network expression correlates with disease progression, disease duration, and clinical severity.

Imaging functional changes at the network level might serve as a powerful tool to monitor treatment effects in future clinical trials and assist to determine new therapeutic targets.

Acknowledgments

The authors wish to thank Ms Yoon Young Choi and Toni Fitzpatrick for invaluable editorial assistance. The work was supported by P50NS071675 (Morris K. Udall Center of Excellence in Parkinson's Disease Research at The Feinstein Institute for Medical Research) and R01NS072514 (Structure-Function Relationships in Dystonia: A Network Approach) from the National Institute of Neurological Disorders and Stroke (to D.E.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the National Institutes of Health.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 513–514).

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KEY POINTS

- Movement disorders should be viewed as circuit disorders that are not confined to localized structural and/or functional abnormalities of the basal ganglia.
- Robust disease and symptom-specific functional brain networks can be identified using different forms of spatial covariance analysis.
- Measurement of functional network activity may be useful as a means of improving the accuracy of differential diagnosis, particularly at early disease stages.
- Changes in network expression precede the onset of clinical symptoms, correlate with disease progression, and can be used to assess the outcome of novel therapeutic interventions for movement disorders.

FIGURE 1.

Effects of subthalamic nucleus (STN) stimulation on network activity during motor learning in Parkinson's disease. (a) Spatial covariance pattern identified by analysis of $H_2^{15}O$ PET scans acquired on and off STN stimulation during the performance of a motor sequence learning task [33^{***}]. The pattern was characterized by increasing activity (red) in the right cerebellum and parahippocampal gyrus, and in the left premotor cortex (PMC) and inferior parietal region. These changes were associated with reductions (blue) in the orbitofrontal cortex (OFC) and the supplementary motor area (SMA). [The network map was overlaid on T1-weighted magnetic resonance-template images. Voxel weights were thresholded at $Z = 2.81$, $P < 0.005$. The display represents regions that were demonstrated to be reliable ($P < 0.05$) on bootstrap resampling (1000 iterations).] (b) Motor learning-related (LEARN) network activity increased during stimulation in 11 of 12 learning trials ($P < 0.008$, permutation test). (c) Baseline regional cerebral blood flow (rCBF) values in the SMA were higher than normal during both sequence learning (LEARN) and motor execution (MOVE) (* $P < 0.05$, ** $P < 0.01$). STN stimulation was associated with a decline in rCBF measured during LEARN ($P < 0.05$) but not during MOVE. Between-intervention [levodopa (LD) vs. deep brain stimulation (DBS)] rCBF differences in this region were significant when recorded during sequence learning ($P < 0.05$); marginal differences ($P = 0.07$) were evident when recorded during motor execution. Derived from [33^{***}] (Figs. 2 and 5).

FIGURE 2.

Tourette syndrome-related pattern (TSRP). (a) This pattern was identified by spatial covariance analysis of FDG PET scans from 12 patients with Tourette syndrome (TS) and 12 healthy controls and characterized by metabolic increases (red) in bilateral premotor cortices and cerebellum covarying with metabolic decreases (blue) in caudate/putamen and orbitofrontal cortices [84*]. (b) Expression of this pattern discriminated patients (triangles) from healthy controls (squares; $P < 0.001$), but did not discriminate between patients with TS with (closed triangles) and without (open triangles) obsessive compulsive disorder (OCD) ($P = 0.80$). The covariance map was overlaid on T1-weighted magnetic resonance template images. The voxel weights for the pattern were thresholded at $Z = 3.09$ ($P = 0.001$) and were demonstrated to be reliable ($P < 0.001$) by bootstrap resampling. Error bar represents 1 SEM. Derived from [84*] (Fig. 1).

FIGURE 3.

Obsessive compulsive disorder-related pattern (OCDRP). (a) This pattern was characterized by metabolic reductions (blue) in the cingulate and dorsolateral prefrontal cortex (DLPFC) covarying with relative metabolic increases (red) in the precuneus and primary motor cortex [84[■]]. (b) The expression of this pattern correlated with Yale-Brown Obsessive Compulsive Scale (YBOCS) scores ($P < 0.005$) and discriminated between the patients with Tourette syndrome (TS) with (closed triangles) and without (open triangles) OCD ($P < 0.05$). The covariance map was overlaid on T1-weighted magnetic resonance template images. The voxel weights for the pattern were thresholded at $Z = 2.33$ ($P = 0.01$) and were demonstrated to be reliable ($P < 0.001$) by bootstrap resampling. Derived from [84[■]] (Fig. 3).