NEUROPSYCHOLOGY THROUGH THE MRI LOOKING GLASS

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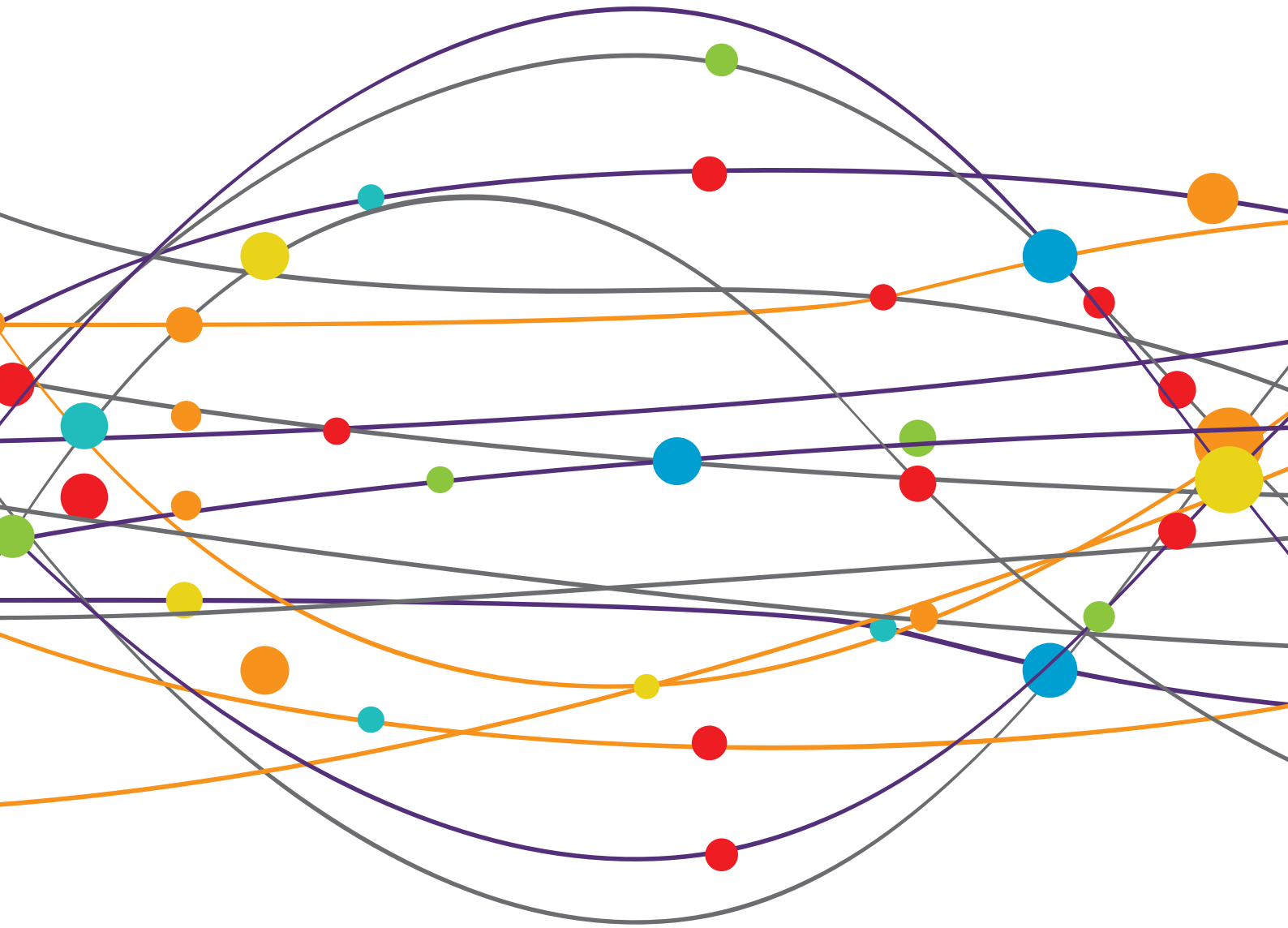

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NEUROPSYCHOLOGY THROUGH THE MRI LOOKING GLASS

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EDITORIAL
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Editorial: Neuropsychology Through the MRI Looking Glass

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Editorial on the Research Topic

Neuropsychology Through the MRI Looking Glass

Since its inception as a science, psychology has been explicitly preoccupied with the mind-body relationship, specifically with the role that the nervous system plays in shaping how we perceive the world around us and how we react in our interaction with it. The evidence in this regard are the second and third chapters of William James's 1890 "The Principle of Psychology" (Volume 1) (1), which explain the functions of the brain and the general conditions underlying its activity, as well as the entire work of Wilhelm Wundt's 1904 "Principles of Physiological Psychology" (2), which explicitly linked the evolution of various mental functions to the organization and physiology of the nervous system. Yet, it was not until 1980s when the neuropsychology has established itself as a branch of psychology in its own right, aiming to explain how the brain and the other parts of the nervous system influence one's cognition, emotions and behaviors using a variety of methods from observation and questionnaires to computerized tasks gathering reaction time and electrophysiology. The knowledge thus obtained in healthy individuals was then employed by neuropsychologists in assessing the impact of various diseases on brain structure and function. The next decade, the 1990s, ushered in the neuroscience era, with the development of various techniques of magnetic resonance imaging (MRI), of which the functional MRI (fMRI) proved to be a key tool in uncovering, *in vivo*, the neurophysiological substrate of specific brain functions. Neuropsychologists quickly incorporated these new techniques in their research methods arsenal and nowadays they are part of the regular curricula in most neuropsychology training programs. In the current Research Topic we sought to gather a group of articles that will showcase the use of various MRI techniques in neuropsychology in both healthy individuals and those affected by different diseases, thus highlighting the specific benefits that MRI can bring in this field.

This Research Topic includes 12 articles that showcase both anatomical (Czekóová et al.; Hlavatá et al.; Liu et al.) and functional (Dash et al.; Fajnerova et al.; Gabitov et al.; Potvin et al.; Qin et al.; Sojka et al.; Solstrand Dahlberg et al.) MRI methods, as well as positron emission tomography (PET) (Longarzo et al.; Trošt et al.), in investigations that range from a case report (Longarzo et al.), to experimental paradigms that involved groups of participants (Czekóová et al.; Dash et al.; Fajnerova et al.; Gabitov et al.; Hlavatá et al.; Qin et al.; Sojka et al.; Trošt et al.), to reviews and meta-analyses (Liu et al.; Potvin et al.; Solstrand Dahlberg et al.). Likewise, the studies included in this special issue sought to investigate the neurophysiological substrates of various brain functions in both healthy individuals and those afflicted by diseases.

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Regarding the use of anatomical MRI in neuropsychology, we showcase here four articles. One of these articles is a case report by Longarzo et al. of a 67-year-old male patient with bilateral thalamic stroke who was investigated using positron emission tomography, magnetic resonance imaging (tractography), and cognitive assessments, performed at baseline and at two follow-up evaluations at 6 and 18 months post-injury. Interestingly, the authors also included 13 healthy individuals matched for age and gender, who followed the MRI protocols of the study. The study presents three major findings: an association between structural and metabolic changes within the fronto-thalamic circuitry in the patient, significant differences between the patient and controls involving the anterior thalamic radiation, one of the major fiber tracts in the fronto-thalamic circuitry and—importantly for clinicians—adaptations to bilateral vascular thalamic injury at multiple levels, revealing the metabolic, functional, and microstructural alterations attending to multidomain neuropsychological impairment. Two articles investigated brain structural differences between patients and their healthy counterparts in conjunction with the results of various clinical neuropsychological assessments. Hlavatá et al. report structural differences in cortical areas related to impulse control in Parkinson's disease patients with and without impulse control disorders (ICD) relative to healthy controls. Moreover, patients without ICD had lower volumes and cortical thickness of bilateral inferior frontal gyrus, whereas those with ICD presented higher volumes of right caudal anterior cingulate and rostral middle frontal cortex. Interestingly, patients with ICD performed no worse than healthy controls in various behavioral tasks previously hypothesized as robust impulsivity measures, thus cautioning against quick interpretation of behavioral tests without additional physiological investigations. Czekóová et al. examined the association between gray matter (GM) atrophy in multiple sclerosis (MS) patients and their performance on tasks measuring several fundamental components of social cognition. They report that patients had slower processing speed, poorer perspective taking, and less imitation compared to healthy controls and that these impairments were associated with GM atrophy in putamen, thalami, and anterior insula, predominantly in the left hemisphere. The last paper in this group comes from a new research area in neuroscience dealing with the microbiota-gut-brain axis. Liu et al. conducted a scoping review of recent studies of healthy individuals and patients with diverse neurological disorders that employed a combination of advanced neuroimaging techniques and gut microbiome analyses. The authors report that gut microbiota profile is significantly associated with markers of brain microstructure, but also with those related to functional intrinsic neural activity and brain connectivity at-rest. These findings highlight the need for longitudinal studies that include assessments of the gut microbial community structure and microbial metabolomics in conjunction with neuroimaging and behavioral testing in order to parse out the directionality and causality within the microbiota-gut-brain axis.

Two articles included PET as imaging technique. One is the case report of the 67-year-old male patient with bilateral thalamic stroke that was already mentioned above (Longarzo et al.). The other is a systematic review of studies that used PET and [^{18}F]-fluorodeoxyglucose (FDG-PET) to investigate changes in brain metabolism in Parkinson's Disease and other α-synuclein pathologies (Trošt et al.). In this review, Trošt et al. conclude that the neuropsychological data in PD and related α-synucleinopathies correlate with metabolic neuroimaging data, thus suggesting that the latter may be used to derive biomarkers of disease progression.

While the remaining seven articles share the fMRI as their main neuroimaging technique, they can be clustered in two main groups based on whether they investigated the brain activity at rest or during tasks.

The group that used resting-state fMRI (rs-fMRI) contains two articles, one assessing the changes in functional connectivity in patients with obsessive-compulsive disorder (OCD) relative to healthy controls and in conjunction with other variables assessed with neuropsychological tests (Fajnerova et al.) and the other investigating the topological organization of different brain networks in patients with type 2 diabetes mellitus (T2DM), again relative to healthy controls and in association with cognitive dysfunction assessed by neuropsychological tests (Qin et al.). In the first article, Fajnerova et al. report altered functional connectivity patterns in OCD patients relative to their healthy counterparts in association with the severity of cognitive and clinical symptoms. In the second article, Qin et al. found changes in topologic properties of several brain networks in T2DM patients relative to healthy controls that were correlated with cognitive performance.

Of the remaining five articles, three used task-related fMRI in original investigations (Dash et al.; Gabitov et al.; Sojka et al.) and two were meta-analyses of original studies that employed the same neuroimaging technique (Potvin et al.; Solstrand Dahlberg et al.). Sojka et al. investigated the brain activity of patients with functional movement disorder (FMD) and matched healthy controls during an emotion regulation task. They report increased activation in FMD patients in several brain areas when observing negative pictures, especially in areas associated with self-referential processing in voluntary emotional regulation and lower emotional awareness. Dash et al. examined the effect of age and bilingualism on the brain networks underlying attentional processes. The authors found an increase in brain activity in the frontal and parietal areas in elderly when compared to young bilinguals, as well as a negative correlation between the proficiency level in the second language and activation level in frontal areas, which was observed only in the elderly group, thus providing evidence for age-related neuroplasticity. Gabitov et al. investigated local and long-distance changes in functional connectivity between areas involved in the acquisition of a motor skill during the course of motor learning in a group of healthy individuals. The authors report task-induced changes in functional connectivity that reflect reconfiguration of the intrinsic connectivity patterns within the somatomotor network during learning, changes that cannot be predicted or detected using the traditional brain activation contrasts.

The last two articles are meta-analyses. In the first article, Potvin et al. conducted a systematic review of schizophrenia literature in order to test the hypothesis that self-disturbances

in schizophrenia may arise from impaired activity in the cortical midline structures and the temporoparietal junction. The authors report that the meta-analysis provided partial support for this hypothesis, with decreased activations only in the dACC and dorsomedial prefrontal cortex, which are involved in cognitive control and/or salience attribution, as well as decision-making, respectively. Given the unexpected decreases in activity in thalamus, which is not a core region of the default-mode network, and is involved in information integration, the authors suggest that the thalamic alterations may compromise self-coherence in schizophrenia. In the second article, Solstrand Dahlberg et al. examined the current fMRI PD literature with the goal of parsing out the contribution of the cerebellum in motor and non-motor functions in this disease. The results revealed that the main cerebellar implications in PD is linked to cognitive functioning, with no significant differences being observed in this structure between PD patients and healthy controls in studies using motor paradigms. Nevertheless, the meta-regression using only data from PD patients indicated that there was a negative correlation between disease severity and cerebellar activation during motor paradigms despite a lack of correlation with disease duration. The authors suggest that these results suggest the presence of a compensatory mechanism to the dysfunctional basal ganglia in PD, where cerebellum may be employed to cope with motor demands.

We believe that the collection of articles grouped in this special issue will increase our awareness of the usefulness of various MRI methods in different areas of neuropsychology. In our opinion, one of the main uses of MRI in neuropsychology is to provide a physiological basis and validation for neuropsychological assessments that are employed in clinical practice. The heterogeneity of the articles in this Research Topic should not be viewed as a feeble, but rather as a strong feature of the research in this field. It highlights the advantages of using the same hardware solution (the MRI scanner), combined with the flexibility of employing various MRI sequences (i.e., structural, functional), data analysis techniques (i.e., model-based, data-driven) and experimental paradigms (i.e., task-based, resting-state) to answer a large diversity of research questions, both fundamental and clinical.

AUTHOR CONTRIBUTIONS

OL and MB wrote the editorial article. Both authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Impaired Self-Other Distinction and Subcortical Gray-Matter Alterations Characterize Socio-Cognitive Disturbances in Multiple Sclerosis

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Introduction: Recent studies of patients with multiple sclerosis (MS) have revealed disturbances in distinct components of social cognition, such as impaired mentalizing and empathy. The present study investigated this socio-cognitive profile in MS patients in more detail, by examining their performance on tasks measuring more fundamental components of social cognition and any associated disruptions to gray-matter volume (GMV).

Methods: We compared 43 patients with relapse-remitting MS with 43 age- and sex-matched healthy controls (HCs) on clinical characteristics (depression, fatigue), cognitive processing speed, and three aspects of low-level social cognition; specifically, imitative tendencies, visual perspective taking, and emotion recognition. Using voxel-based morphometry, we then explored relationships between GMV and these clinical and behavioral measures.

Results: Patients exhibited significantly slower processing speed, poorer perspective taking, and less imitation compared with HCs. These impairments were related to reduced GMV throughout the putamen, thalami, and anterior insula, predominantly in the left hemisphere. Surprisingly, differences between the groups in emotion recognition were not significant.

Conclusion: Less imitation and poorer perspective taking indicate a cognitive self-bias when faced with conflicting self- and other-representations. This suggests that impaired self-other distinction, and an associated subcortical pattern of GM atrophy, might underlie the socio-cognitive disturbances observed in MS.

Keywords: multiple sclerosis, social cognition, self-other distinction, automatic imitation, visual perspective taking, voxel-based morphometry, gray-matter volume

INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system. As part of a complex neurological symptomatology, MS patients present frequently with disturbances in various aspects of cognitive functioning; slower processing speed, impaired episodic memory and executive function are among the most affected (1, 2). Another domain in which dysfunction manifests is social cognition (3)—that is, the broad repertoire of cognitive and affective skills that allow us to infer others' mental and emotional states in order to interact with them effectively (4, 5). Patients' quality of life is reduced considerably by disruptions to their social environment, and so the development of effective interventions requires a better understanding of the socio-cognitive deficits that impact negatively on their interpersonal relationships. Since the range of abilities comprising social cognition span various levels of complexity, however, a precise characterization of these impairments is difficult with standard neuropsychological tests (6).

Unlike the long history of research into general cognitive impairments in MS, only recently have studies begun to unveil the nuanced nature of disturbances in social cognitive abilities exhibited by these patients. The findings of these studies often converge to reveal difficulties in lower-level capacities, particularly in the recognition of negatively valenced facial emotions [e.g., sadness, anger, fear; (7)]. In contrast, investigations of other higher-level components of social cognition provide less consistent insights; while some report that patients are impaired in their ability to attribute mental ("mentalizing") *and* affective states to others ["empathy"; (8, 9)], other studies have observed disturbances only in cognitive mentalizing (10, 11). Moreover, it remains to be seen whether impairments in these high-level facets of social cognition result from disruptions to more fundamental components.

Although the precise structure of social cognition is yet to be defined, current research suggests a hierarchical organization in which lower-level mechanisms contribute to or provide a necessary prerequisite for higher-level processes (4). In this model, mentalizing is believed to build upon a more fundamental ability to take another's perspective. Consistent with this notion, both perspective taking and mentalizing engage the superior temporal/temporo-parietal cortices [e.g., (12)]. Similarly, emotion recognition is considered a necessary prerequisite of empathy, and both processes are associated frequently with brain responses within the insulae and anterior cingulate cortex (13–15). More recently, we have shown that empathic expression is mediated by imitative tendencies, suggesting that a process of emotional simulation might be necessary for empathy (16).

Furthermore, multiple components of social cognition are thought to recruit a common mechanism of *self-other distinction* (SOD), which enables us to treat independently and distinguish flexibly between cognitive self and other representations (15, 17). Without efficient SOD, we might egocentrically misattribute our own cognitive and affective states onto others. This would be evident particularly when our own self states are incongruent with those of others (18), resulting in poor emotion recognition and empathic awareness, and inappropriate responding in social situations. Since the viewpoints of other individuals often conflict with our own, this mechanism is also necessary when inferring our interaction partners' perspective—adopting another's perspective requires us to detach ourselves from our own representations (19). On the other hand, dysfunction to this low-level cognitive mechanism might result in uncontrolled self-other merging. Humans exhibit an involuntary tendency to mimic one another during social interaction (20), which appears to reflect a common neural coding of self- and other-action [e.g., (21)]. Control of imitative tendencies therefore requires SOD to differentiate between our own and others' actions (17, 22); without this mechanism, we might exhibit hyperimitation [see (17)]. Consistent with the notion of SOD providing a mechanism common to both perspective taking and mimicry, past research has demonstrated that the expression of involuntary imitation is related inversely to perspective-taking performance (23, 24). Moreover, SOD is associated frequently with brain activity in the temporo-parietal cortices (15). Disturbances to SOD might therefore underlie the higher-level socio-cognitive deficits observed in MS.

Traditionally, MS has been characterized in terms of white matter (WM) pathology, but recent research indicates that gray matter (GM) abnormalities can predict dysfunctional social cognition in this patient population (25). GM atrophy within deep nuclei and the limbic system is present in the very early stages of MS (26), and progresses rapidly in all MS phenotypes (27). This is observed in the thalamus, putamen, caudate nucleus, globus pallidus, and amygdala (26, 28). While other brain regions are associated more frequently with social cognition, these subcortical structures do appear to play an important role in socio-cognitive functioning; the limbic and paralimbic system (including amygdala, striatum, temporal pole, and anterior cingulate) have been implicated in representation of self and other mental states, for instance, and the dorsal striatum has been associated with cognitive mentalizing (29). Correspondingly, disturbances in social cognition also comprise the symptomatology of Parkinson's and Huntington's disease—disorders characterized partly by disruptions to cortico-basal ganglia-thalamo-cortical circuits [e.g., (30)]. Focal GM atrophy among these structures might therefore contribute to the deficits in social cognition exhibited in MS. Unfortunately, however, the majority of research in MS has been performed exclusively at the behavioral or self-report level (8, 9, 11, 31), with relatively few studies combining this with neuroimaging data (25, 32, 33).

To achieve a better characterization of the disturbances in social cognition exhibited by MS patients, the present study utilized three experimental tasks designed to measure discrete, low-level socio-cognitive capacities; specifically, in line with the model described above (4) we measured emotion recognition, visual perspective taking, and imitative tendencies. To assess perspective taking, we measured patients' performance on a task that required them to infer other person's viewpoint when it is incongruent with their own. To examine emotion recognition we assessed their ability to infer the emotional state

TABLE 1 | Sample demographics and clinical characteristics.

	Groups		
	MS	**HC**	***P***
Age (mean [SD])	35.8 (8.0)	34.7 (11.0)	0.585
Males	12 (28 %)	18 (42 %)	0.175
EDSS (median [range])	2.5 (6)	–	–
DD (mean [SD])	7.5 (4.4)	–	–
LQ (median [range])	100 (120)	100 (200)	0.177
University degree	24 (56%)	43 (100%)	<0.001

of another person from just their eyes. Finally, to quantify imitative tendencies we measured the degree to which they imitated the actions of another person automatically, even when this interfered with another task. Using GM volume (GMV) as a metric of brain structure, we then applied voxel-based morphometry to examine whether any of these behavioral indices of social cognition were related to patterns of neural atrophy. Given that MS is associated frequently with a pattern of GM atrophy throughout deep subcortical nuclei, and the apparent role of these nuclei in social cognition, we hypothesized that the degree of GM reduction throughout subcortical brain structures would be related positively to disruptions of SOD.

MATERIALS AND METHODS

Sample

We recruited 43 patients with relapsing-remitting MS consecutively from the Department of Neurology at St. Anne's University Hospital, Czech Republic, and 43 healthy controls (HCs) matched on age, sex, and handedness (for details on demographics, see **Table 1**). Handedness was assessed with the revised version of the Edinburgh Handedness Inventory (34); a laterality quotient (LQ) was calculated as (right–left)/(right + left) × 100. Physical disability was assessed in MS patients with the Expanded Disability Status Scale [EDSS; (35)]. All patients had been diagnosed according to the revised McDonald criteria (36), and had no other neurological or psychiatric diagnoses. Patients reporting mild to moderate depressive symptoms were included in the study, but the extent of symptoms reported by the two groups were not statistically different (see below). The minimum duration in education was 12 years (i.e., completion of secondary education). Importantly, the availability of disease-modifying treatment for MS patients in the Czech Republic is currently limited to those meeting certain criteria. For this reason, only 36 of these asymptomatic patients (84%) were undergoing treatment: interferon beta 1a ($n = 9$), interferon beta 1b ($n = 3$), fingolimod ($n = 6$), glatiramer acetate ($n = 6$), dimethyl fumarate ($n = 6$), teriflunomide ($n = 3$), natalizumab ($n = 2$), and daklizumab ($n = 1$). The experiment was approved by the Institutional Review Board of St. Anne's University Hospital, and all individuals provided written informed consent prior to participating.

Procedure

Participants underwent behavioral assessment prior to brain scanning, which took place no longer than seven months afterwards (M = 5.2 months; SD = 1.6). Importantly, no relapses were presented during these examination periods. The test battery was performed in a single session lasting ∼1 h, with each assessment administered in the order in which they are described below. Implicit task-performance measures were obtained before explicit and self-report assessments so that the latter could not influence the former.

Cognitive Processing Speed

To screen for possible cognitive impairment, we employed a paper version of the Symbol Digit Modalities Test [SDMT; (37)]. This test has been established as a reliable and valid measure of cognitive processing speed in MS patients, and the best predictor of cognitive dysfunction in this population given the influence of processing speed on other cognitive functions (38, 39).

Imitative Tendencies

To measure imitative tendencies we employed a computerized stimulus–response compatibility procedure (40), whereby participants are required to execute finger-lifting actions in response to a colored dot (imperative stimulus) while observing task-irrelevant finger actions performed by a stimulus hand (**Figure 1A**). The degree to which participants are faster and more accurate at executing finger movements signaled by the imperative stimulus when they observe simultaneous matching (compatible) compared with opposing (incompatible) movements is referred to as automatic imitation, and is considered an experimental measure of spontaneous mimicry; higher scores represent greater imitative tendencies. Importantly, Genschow et al. (41) report high split-half reliability (0.86) for this compatibility effect.

All trials began with a warning stimulus, comprising a model's pronated right hand with all fingers resting on a flat surface but rotated 90° counter-clockwise from the participants' perspective. At this point, the participant depressed both the left and right directional arrows on a standard keyboard with the index and middle finger of their right hand, respectively. After 800, 1,600, or 2,400 ms, selected randomly, the warning stimulus was replaced with an end-point image of the same stimulus hand performing either an index or middle finger extension. In this end-point image, a red or green dot was presented between the index and middle finger. The color of this dot signaled whether the participant should move their own index or middle finger (e.g., green = index finger, red = middle finger; the color-finger pairing was counterbalanced across participants). In response to the imperative stimulus, the participant lifted the corresponding finger as quickly as possible, thereby releasing a key. The trial then ended with a blank screen lasting 1,000 ms. The task consisted of three trial types: compatible (the same finger action was signaled and observed), incompatible (opposite finger actions were signaled and observed), and baseline (movement was signaled but not observed). Overall, the paradigm comprised 70 trials—30 compatible, 30 incompatible, and 10 baseline trials—with accuracy and response time (RT) measured on each trial.

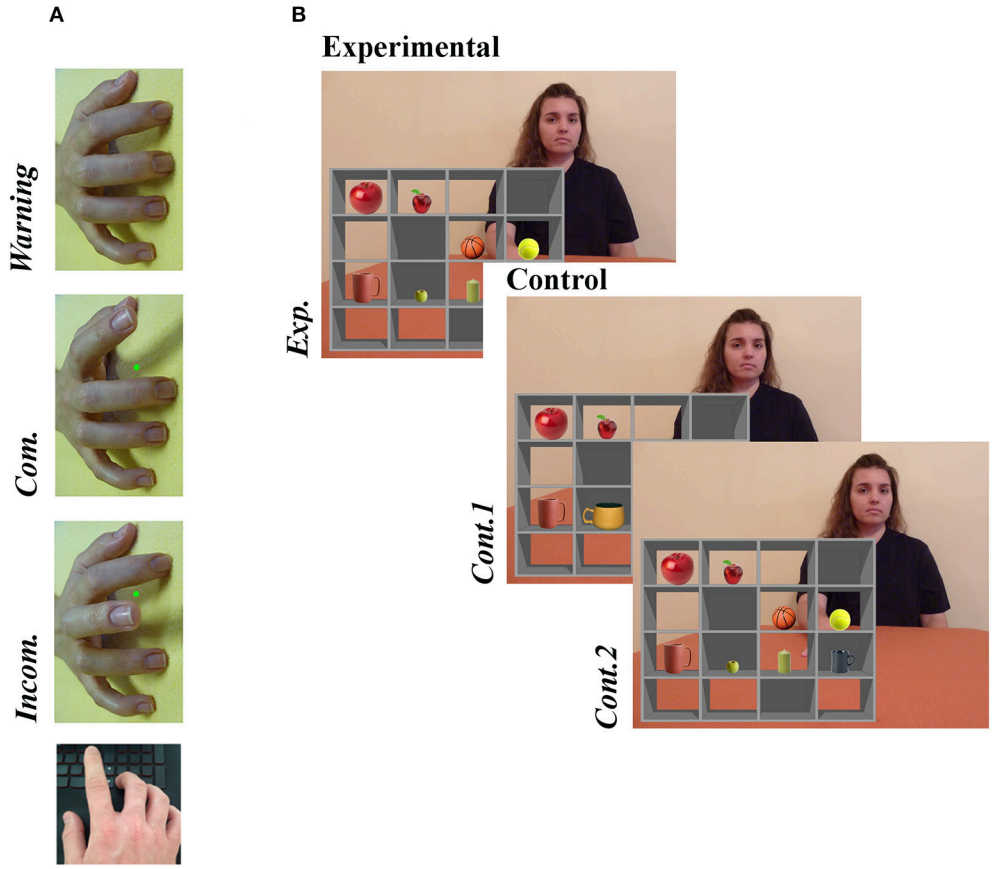

FIGURE 1 | Examples of experimental stimuli for **(A)** the Stimulus-response compatibility procedure and **(B)** the Director Task. **(A)** A right stimulus hand was presented at a 90° counter-clockwise rotation. In this example, a green dot (imperative stimulus) signals that the participant should lift index finger. Whether the observed finger movement was the same or different to the one signaled by the imperative stimulus defined the condition (Compatible [*Com.*] or Incompatible [*Incom.*], respectively). **(B)** An audible instruction given by the Director asked the participant to move one of the items to a new box (*"Move the smallest apple one box down"*). On experimental trials (*Exp.*), the instruction referred to an object that created a discrepancy between the Director's and participants' perspectives, while no such discrepancy existed on control trials; no distractor object was present in *Cont. 1*, and in *Cont. 2* the instruction referred to a different object (*"Move the biggest apple one box down"*). Written informed consent was obtained from the individual for the publication of this image. For full instructions, see the **Supplementary Information**.

It is important to emphasize that we used a right stimulus hand rotated 90° counter-clockwise. Since participants responded with their right hands, this stimulus isolated imitative- from any confounding spatial-compatibility effects to provide a pure measure of imitative tendencies (24).

Perspective Taking

The Director task was used to assess individuals' ability to differentiate between their own visual perspective and that of another when the two viewpoints conflict [visual perspective taking; e.g., (42)]. Recently we observed that both RTs and accuracy demonstrated excellent split-half reliability in each condition [> 0.96; (16)].

As illustrated in **Figure 1B**, the stimulus consisted of a grid of shelves forming 16 boxes, with a different object placed in each of eight boxes. On each trial, the participant received a recorded verbal instruction from a female "Director" to move one of the objects to a different box. The Director sat behind the shelves and therefore could not see the contents of five boxes with opaque backs, which were visible only from the participant's (front) perspective. On experimental trials, the instruction referred to an object that created a discrepancy between the Director's and participants' perspectives (e.g., *"Move the smallest apple one box down,"* when the director could see only the medium-sized apple). To perform the instruction correctly on these experimental trials, the participant had to discount any "distractor" objects not visible to the Director (e.g., they were required to move the medium-sized apple rather than the smallest). In both control conditions, there was no conflicting object to discount: the distractor was replaced with a non-conflicting object in the first control condition (Cont.1), and in the second (Cont.2) the Director's instruction changed so as to render the distractor irrelevant (e.g., "*Move the biggest apple one box down*"). Each condition comprised 20 trials presented randomly. The audio recordings of instructions were equivalent across all trials [mean 3.26 (SD .22) sec]. Participants responded by clicking with the

mouse on the box where the object should be moved. Errors involved selection of the wrong (e.g., distractor) object or wrong location, the latter including omission of left–right switching (moving the target object left one box when they were instructed to move it rightwards, or vice versa). Any potential difference in perspectives was emphasized on practice trials that included a front and rear view of the shelves (see **Supplementary Material** for instructions given to participants).

Emotion Recognition

A paper version of the Reading the Mind in the Eyes Test [RMET; (43)] was employed to measure participants' ability to infer the emotional state of others. Although the task is employed frequently as a measure of affective mentalizing, it is considered by some scholars to measure only the first stage of this process—emotion recognition (44). This task contains 36 images depicting the eye region of actors' emotional facial expressions. Facial expressions represent complex emotional states with positive (e.g., playful, interested), negative (e.g., hostile, suspicious), and neutral valence (e.g., reflective, pensive). Each image is presented sequentially, and participants are required to select one of four labels that best match the expression without a time limit. A sum of correct responses is used as a measure of success.

Depression

All participants completed the Beck Depression Inventory [BDI-II; (45)]. Using 21 items, this self-report instrument assesses cognitive, affective, physiological and motivational symptoms of depression experienced over the preceding 2 weeks. Scores of 20–28 indicate moderate depression. The BDI-II has been found to be a valid and reliable instrument for the evaluation of depressive symptoms in MS (46).

Fatigue

Patients and controls completed the Modified Fatigue Impact Scale [MFIS; (47)], a self-report instrument that assesses the degree to which physical, cognitive, and psychosocial fatigue experienced over the preceding 4 weeks has affected everyday functions.

MRI Acquisition

High-resolution T1-weighted anatomical images were acquired on a 1.5T Siemens Symphony scanner, using a standard 32-channel array head coil and an MPRAGE sequence: 176 sagittal slices (slice thickness = 1.17 mm); TR = 1,700 ms, TE = 3.93 ms, TI = 1,100 ms, flip angle = 15°; in plane matrix size 256 × 256, resampled to 512 × 512, FOV = 246 × 246 mm, in-plane resolution = 0.48 × 0.48 mm.

Statistical Analyses

Behavioral Data

Differences between the groups were assessed using parametric or non-parametric *t*-tests, depending on the normality of variable distributions. Independent-samples *t*- and Mann-Whitney *U*-tests were employed to contrast MS patients with HCs. Since normality was violated for the majority of the variables, associations between them were examined by Spearman correlation coefficients, all of which were entered into a multivariate bootstrapping procedure (1,000 iterations) to obtain 95% confidence intervals (CIs). These intervals provide an estimate of population values for each coefficient, providing an alternative measure of significance; CIs including zero should be considered unreliable.

For calculating measures of imitative tendencies and perspective taking, we employed an approach that we have used previously to investigate relationships between these two components of social cognition (16, 24). The strength of imitative tendencies was expressed as the difference in response time (RT) between the incompatible relative to the compatible condition, and perspective-taking performance was expressed as the difference in RT and accuracy on the experimental relative to the control conditions. Importantly, there was no evidence of a speed-accuracy trade-off for perspective taking in this sample ($p = 0.165$), so relative measures for RT and accuracy scores were calculated separately. For both measures, responses on the control condition were regressed from those in the corresponding experimental condition(s), resulting in residualized scores that reflect the difference between the conditions: specifically, greater residuals reflect poorer performance (slower RTs and poorer accuracy in the experimental relative to the control conditions. It is important to emphasize that measures of both imitation and perspective taking are relative (RTs on incompatible *vs.* compatible trials, and experimental *vs.* control trials, respectively), and should therefore be uninfluenced by any differences in processing speed between MS patients and HCs. The statistical analyses were performed using SPSS 24 software.

Neuroimaging Data

To compare GMV between the brains of HCs and MS patients we analyzed MR images with the optimized VBM pipeline provided in FSL (48). This analysis pipeline produces results that converge closely with those from the Statistical Parametric Mapping platform (49).

First, the anatomical images were brain-extracted and segmented into GM, WM and cerebrospinal fluid using *FAST* (50), and the resulting GM partial-volume maps were affine-registered to the MNI-152 standard space template using *FLIRT* (51). The registered GM images from the entire sample (both HCs and MS patients) were then concatenated and averaged, and flipped along the x-axis. By re-averaging each mirror image to the MNI-152 template, a first-pass left-right symmetric, study-specific "affine" GM template was created. This step avoids introducing any bias during the registration process. Second, all native GM images were re-registered non-linearly to the affine template with *FNIRT* (52), concatenated, averaged, and flipped along the x-axis. Symmetric, study-specific "non-linear" GM templates were then created by averaging both mirror images, and native GM partial-volume maps were registered to their corresponding non-linear template. Importantly, this optimized protocol modulates each registered GM image to compensate for any contraction/enlargement due to the non-linear transformation; specifically, each voxel of each image was multiplied by the Jacobian of the warp field [see (53)].

Since this modulation does not include the affine part of the registration, however, no correction for total intracranial volume is needed (48). The modulated GM images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm.

General Linear Modeling (GLM) was then applied to the resampled, smoothed and modulated GM images to assess localized differences between the HC and MS group. Since MS is characterized by localized WM lesions, appearing as hypointensities on T1 images that can result in an overestimation of GMV, we added to these group comparisons a covariate of no interest representing subject-specific values of mean WM calculated from the corresponding partial-volume map. Subsequently, by adding measures from patients' clinical assessment or behavior on each experimental task as covariate regressors in further GLM analyses, we examined whether localized GMV in the MS group was related to clinical characteristics or socio-cognitive performance. Using *randomize* (37), all resulting statistical maps were thresholded with permutation-based non-parametric inference; 5,000 permutations were performed with threshold-free cluster enhancement (54), and family-wise error (FWE)-corrected for multiple comparisons.

RESULTS

The values below present means (±SD).

Clinical Assessment

The MS patients performed worse than the HCs on the SDMT (56.42 [±9.26] vs. 69.21 [±10.00]; $t_{(84)} = 6.154$; $p < 0.001$, $d = 1.33$), and reported greater fatigue on the MFIS (29.65 [±12.99] vs. 18.72 [±13.59]; $U = 518.00$; $p < 0.001$; $r = 0.38$). Although the MS group also expressed more depression (10.53 [±8.20] vs. 7.35 [±6.06]), this difference was not statistically significant ($p = 0.055$; $r = 0.21$; see **Figure 2A**).

Behavioral Performance

Five MS patients and three HCs were excluded from the analyses of perspective-taking performance because they achieved a score of zero in the experimental condition of the Director Task, suggesting a misunderstanding of task instructions. Both imitation and perspective taking differed between the groups: compared with HCs, patients showed significantly less imitation (23.78 [±30.22] vs. 38.97 [±32.89] ms; $t_{(84)} = 2.23$, $p = 0.028$; $d = 0.48$), and both longer response time (0.21 [±1.14] vs. −0.20 [±0.79]; $U = 525.00$, $p = 0.019$; $r = 0.27$) and poorer accuracy in perspective taking (−0.20 [±0.97] *vs.* 0.20 [±0.99]; $U = 649.00$, $p = 0.017$, $r = 0.26$). Surprisingly, however, emotion recognition was similar in the MS patients and HCs (24.74 [±3.44] vs. 25.81 [±3.57]); $U = 731.50$, $p = 0.094$; $r = 0.18$; See **Figures 2B,C**).

Correlations between the clinical assessments and socio-cognitive measures revealed significant relationships only between disease duration and accuracy in perspective taking ($\rho_{(36)} = -0.36$; $p = 0.026$; CI = [−0.62, −0.06]). No associations emerged with respect to other measures of social cognition ($p \geq 0.086$), or self-reported fatigue and depression ($p \geq 0.257$; see **Table S1**). As expected, there were no significant relationships between cognitive processing speed (SDMT scores) and any measure of socio-cognitive performance ($p \geq 0.217$, see **Table S2**).

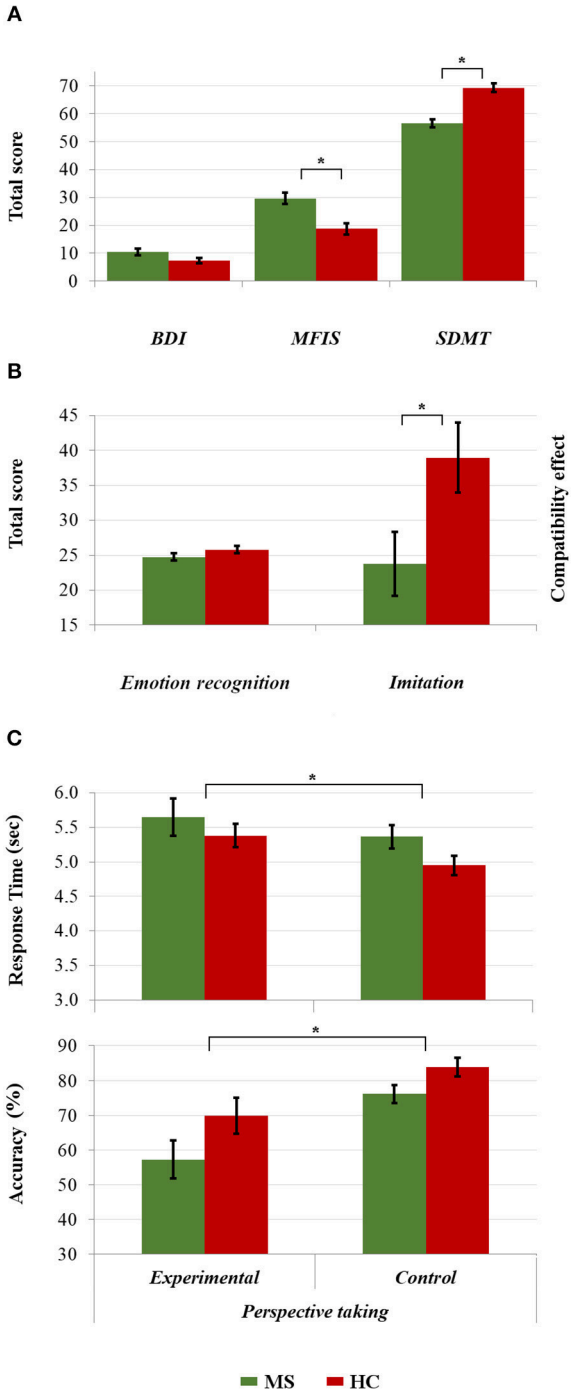

FIGURE 2 | Comparisons between the HC and MS group in **(A)** clinical assessment and cognitive processing speed, **(B)** emotion recognition and imitative tendencies, and **(C)** response time and accuracy in visual perspective taking. *$p < 0.05$.

TABLE 2 | Results of voxel-based morphometry analyses, presenting peak voxels of clusters in which gray matter volume was higher in the HC relative to the MS group (HC > MS; $p_{FWE} < 0.01$), or associated with imitation (IMI), perspective-taking performance (VPT) or clinical characteristics (EDSS; $p_{FWE} < 0.05$).

	Label		# Voxels	Peak	x	y	z
HC > MS	Thalamus	R	10638	5.00	15	−26	3
	Insula/opercular cortex	R	2532	4.52	47	5	1
	Temporal pole	R	1740	4.68	40	10	−32
	Planum temporale	R	1168	4.16	55	−25	13
	Caudate nucleus	L	160	4.06	−20	3	17
	Insula (posterior)	R	25	3.28	40	−16	−2
IMI	Thalamus	L	236	3.73	−10	22	10
	Insula (anterior)	L	5	3.47	32	24	10
VPT	Putamen	L	8	3.23	−26	4	−8
EDSS	Amygdala	L	59	4.02	−22	−4	−14
		R	40	4.54	16	−4	−14
	Caudate	L	40	4.54	16	−4	−14

Neuroanatomy

A whole-brain GLM analysis revealed a diffuse collection of cortical and subcortical regions in which GMV was reduced in MS patients relative to HCs, after accounting for variability in mean WMV ($p < 0.01$, FWE-corrected): this encompassed right lateral temporal cortex and the amygdala; and the bilateral amygdala, caudate nucleus, pallidum, putamen, thalamus, and hippocampus. We refer to this herein as $GM_{overall}$, and these results are presented in **Table 2** and **Figure 3A**. Interestingly, only cognitive processing speed (SDMT scores) was related with $GM_{overall}$–higher processing speed was associated with more GMV throughout this pattern of brain regions ($\rho_{(41)} = 0.36$, $p = 0.019$; CI = [0.01, 0.63]; see **Figure 4A**).

When adding clinical measures as covariates in GLM analyses of MS patients, neither disease duration nor SDMT scores showed significant associations with localized GMV. Scores on the EDDS, however, were associated negatively with GMV in the bilateral amygdalae and left caudate nucleus ($p < 0.05$, FWE-corrected). In terms of performance on the experimental tasks, accuracy in perspective taking was associated positively with GMV in a small ventral aspect of the left putamen ($N = 38$; $p < 0.05$, FWE-corrected). To investigate relationships between brain structure and behavior on the tasks expressed as response time, we added SDMT scores as an additional covariate of no interest; although we observed no significant relationships between task performance and cognitive processing speed, this allowed us to identify brain-behavior relationships that were independent of general processing speed. Response times in perspective taking showed no significant associations with GMV, but the degree of imitative tendencies demonstrated on the stimulus–response compatibility procedure was associated positively with GMV in a large portion of the left thalamus and left anterior insula cortex ($N = 43$; $p < 0.05$, FWE-corrected). These results are presented in **Figure 3B** and **Table 2**, and **Figure 4** plots selected significant brain-behavior relationships across the MS sample.

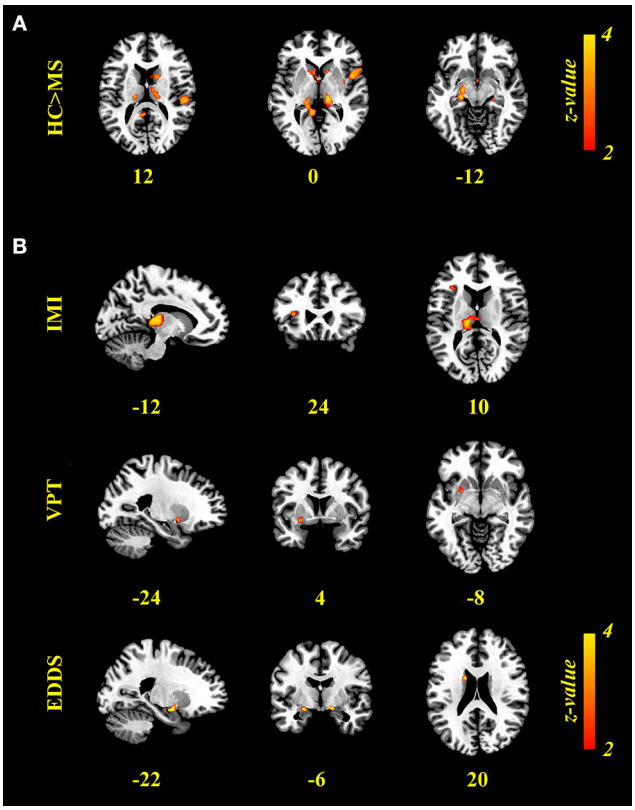

FIGURE 3 | Results of voxel-based morphometry (VBM) analyses. **(A)** Brain regions expressing greater gray-matter volume (GMV) in the HC relative to MS group ($p < 0.01$, FWE-corrected). **(B)** Brain regions in which GMV was associated positively with imitation measured on the Stimulus-response compatibility procedure (IMI) and accuracy of visual perspective taking on the Director Task (VPT), and negatively with clinical scores (EDDS; $p < 0.05$, FW-corrected). VBM results are presented on the Colin template in MNI space, neurological orientation, with values presenting the *x*, *y*, or *z* coordinate of the corresponding slice.

Finally, since our sample varied in achieved education level (see **Table 1**), we investigated whether this might have influenced the above findings; specifically, we compared both GMV and behavioral performance between the 19 patients with secondary school education and 24 with university degrees. Using the exact same parameters with *randomize*, no significant differences were observed between these two patient subgroups. The same (null) result was obtained when contrasting cognitive, socio-cognitive, and self-report scores ($p \geq 0.140$).

DISCUSSION

This study sought to achieve a better characterization of the disruptions to social cognition observed in MS by investigating lower-level facets of socio-cognitive abilities, and examining the neuroanatomical correlates of any impairments. Our findings indicate that, behaviorally, patients with relapse-remitting MS exhibit less involuntarily imitation toward the actions of others compared with HCs, and find it more difficult to adopt

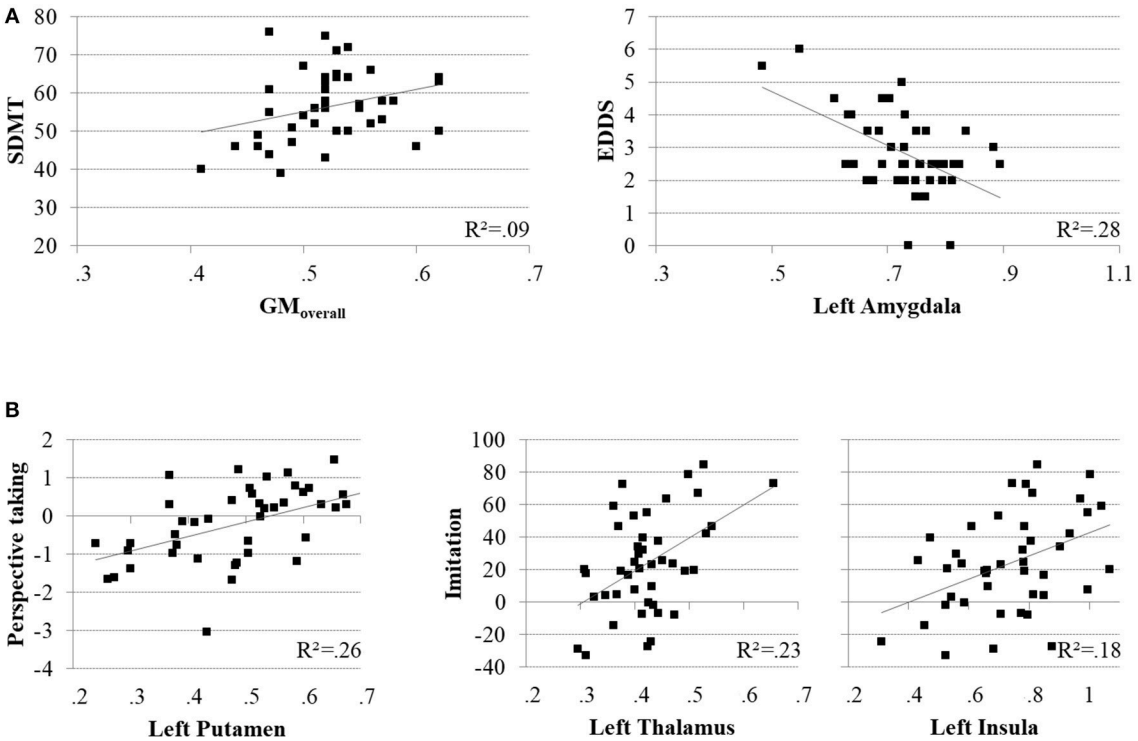

FIGURE 4 | Scatter plots illustrating significant brain-behavior relationships for the MS group. **(A)** Positive association between cognitive processing speed (SDMT) and the overall pattern of relative GMV decline ($GM_{overall}$; left), and negative association between EDSS scores and GMV in the left amygdala (left). **(B)** Positive associations between accuracy in perspective taking and GMV in the left putamen (left), and imitative tendencies and GMV in the left thalamus (middle) and left insula (right).

another individual's perspective when it differs from their own. Furthermore, this behavioral pattern is associated with reduced GMV in the patient group within deep brain nuclei, revealing a potential neuroanatomical correlate.

To our knowledge, this is the first neurobehavioral investigation of imitative tendencies and visual perspective taking in a neurological population. On the basis of our own and others' previous research, we interpret the pattern of behavior exhibited by our sample of MS patients to reflect impaired self-other distinction [SOD; (4, 16, 24)]. Efficient perspective-taking performance is shown by individuals who can switch flexibly between altercentric and egocentric viewpoints, and report a balanced attentional focus between the self and others during social interactions (55). In contrast, MS patients appear to fall back on a default cognitive state of self-bias when faced with competing self- and other-representations (56)—they appear to be less able to detach themselves from their own self-perspective in order to infer conflicting viewpoints. Likewise, MS patients are less influenced by others' actions. Interestingly, we observed the same pattern of behavior in a large healthy sample; specifically, poorer perspective taking and reduced imitation was observed in individuals characterized by an inflexible personality profile compared with those exhibiting more flexibility (16). In this light, the disturbances presented by MS patients in high-level socio-cognitive capacities, such as mentalizing, might reflect dysfunction to a more fundamental, low-level cognitive mechanism responsible for distinguishing flexibly between self and other representations.

In contrast to previous research (8, 25, 57), MS patients performed equally as well as HCs on a task measuring emotion recognition (RMET). While this might indicate that emotion recognition is preserved in this sample of MS patients, it may simply highlight an important difference between the three experimental tasks we employed; namely, their differential requirements for fast and flexible switching between self and other representations: While successful performance on the Director Task (DT) and Stimulus-response Compatibility (SRC) procedure necessitates swift SOD, the RMET involves a selection of one of four choices describing the mental states expressed by eyes, placing less demands on SOD flexibility. In a similar vein, differential performance on these tasks could result from their different demands on executive function; both the DT and SRC procedure are essentially response inhibition tasks, whereby successful performance necessitates the speeded selection of relevant and suppression of irrelevant information [e.g., (58)]. This is less true of the RMET. Indeed, we suggested that individual differences in cognitive control might underlie the opposing behaviors we observed previously between flexible and inflexible personality profiles (16). It is particularly noteworthy that we also observed equivalent empathic responses between

these two profiles. Since the present study did not perform a thorough assessment of executive functioning in MS patients, we are unable to make further claims about its influence of SOD. However, recent research points to the functional independence of executive dysfunction and impairments to social cognition in the MS population [see (59)].

In line with previous research, our measures of social cognition were not associated with self-reported depression (3, 7–9), fatigue (11), or cognitive decline [(8, 11); but see (3)]. This suggests that these frequent symptoms of MS do not predict disturbances in social cognition on their own. Additionally, we observed no relationships between physical disability and our measures of socio-cognitive performance. In contrast, poorer accuracy in perspective taking was associated with disease duration.

Turning now to our neuroanatomical findings, the pattern of GMV reduction we have observed in MS patients aligns closely with previous studies; these structural alterations occurred in the thalamus, putamen, caudate nucleus, globus pallidus, and the amygdala, structures in which GM atrophy frequently appears first and progresses rapidly (26–28). Furthermore, relationships between gray matter and task performance in a selection of these deep brain structures implicate them in the socio-cognitive impairments exhibited by MS patients; reduced GMV was associated with poorer perspective taking in the left putamen, and reduced automatic imitation in the thalami and the left anterior insula (AI), independent of cognitive processing speed. Although the neuroanatomical basis of socio-cognitive disturbances in MS remains understudied (60), these results do converge with studies in the healthy population: First, brain function within the dorsal striatum is reported during the cognitive aspect of mentalizing (29), when differentiating between social actions performed by the self and others, and when processing social behavior in general (61). Second, recent research indicates that intact functioning of thalamus is critical for dynamic integration of information across various cortical networks (62), including those implicated in socio-cognitive and -affective processes [e.g., mentalizing; see (29)]. Interestingly, this region seems to be integral for behavioral flexibility (63)—a role that may extend to flexible self-other switching. Third, previous research has associated brain function within the AI with imitative tendencies (5), as well as processes of interoception, empathy, and social awareness (64). Although the majority of existing studies have linked AI with affective components of social cognition, the left AI has been reported to be activated by both emotional and cognitive aspects (13).

It is noteworthy that all GM areas associated significantly with social cognition were localized primarily to the left hemisphere. Although this observation is in line with other findings reporting a predominantly left-lateralized network of brain regions associated with other aspects of social cognition (65), research into the lateralization of disturbances exhibited by MS patients remains scarce and inconsistent (25); socio-cognitive processes have been related to GMV throughout both left and right hemisphere (33, 65). Interestingly, previous research has indicated that cognitive flexibility is associated with brain regions in the left hemisphere (66), while self-referential processing is linked primarily with the right (67). As such, it might be that our results reflect a selective deficit of cognitive flexibility and preserved self-processing. This finding, then, presents a new avenue of investigation in MS.

Given the potential for functional neuroimaging as an evaluative tool for the early detection of brain alterations in MS, future studies should explore the brain networks engaged by the two experimental tasks we have used to reveal disruptions in SOD. It is important to acknowledge that we have investigated GM volume in what is primarily a WM disorder. While patterns of GM pathology appear to be associated more heavily with cognitive dysfunction in MS than concomitant WM lesions (68), diffuse WM abnormalities are likely to result in the disconnection of brain networks supporting social cognition (32). Interestingly, Plata-Bello et al. (69) report decreased functional connectivity in the brains of MS patients relative to HCs during action observation/execution. Future research should investigate whether the subcortical pattern of GMV reduction that we have observed in MS is related to a loss of WM integrity.

It is important to acknowledge aspects of our study that might limit the generalization of the present results. First, we examined only one index of cognitive functioning—scores on the SDMT. Although this is considered a gold-standard screening tool in MS, and a reliable predictor of cognitive decline in MS (38, 39), we were unable to explore relationships between social cognition and other, more general cognitive domains. As alluded to earlier, the DT and SRC procedure are believed to require response inhibition (58). A more detailed neuropsychological examination of cognitive performance might provide better insights into the relationship between this aspect of executive function and low-level components of social cognition. Second, the group of MS patients recruited in this study differed significantly in their level of educational attainment from those in the HC group. While this difference did not manifest in either behavioral performance or our metric of brain structure, the results of the present study should be treated with caution until they are replicated in comparisons of more educationally balanced MS patients and healthy controls. Third, behavioral assessment was performed 5 months prior to brain scanning on average. While substantial GM atrophy is unlikely to occur during this time interval in MS patients with cognitive reserve (70), it is possible that new WM lesions could have developed. On a related note, because this study recruited a sample of asymptomatic MS patients, a non-routine MRI protocol was performed that involved the acquisition of only T1-weighted images. Lesions of WM appear as hypointensities on T1 images, resulting potentially in an overestimation of GMV. We have attempted to control for this by adding estimates of total WMV calculated from the same T1 image as a covariate of no interest. This is a crude approach, however, and much more accurate methods are available; with the addition of T2-weighted images, automated WM lesion-detection tools (71) can provide accurate estimates of focal lesion load, allowing for lesion masking that improves volumetric estimation [e.g., (25)]. As such, although the brain-behavior relationships we have observed in the present study converge

closely with previous research, our findings require replication in future research that addresses these limitations.

In conclusion, our study revealed a potential low-level cognitive mechanism underlying the socio-cognitive disturbances exhibited by patients with MS; at the behavioral level, the performance of MS patients indicated increased self-bias when faced with conflicting self- and other-representations—while emotion recognition seems to be preserved, they showed poorer perspective taking and less involuntary imitation. These selective behavioral impairments were associated with a pattern of reduced GMV that encompasses deep brain nuclei, pointing toward a neuroanatomical correlate for this socio-cognitive profile. Future research should build on our findings by clarifying the influence of structural alterations in these discrete brain structures on SOD, and how this manifests in other socio-cognitive capacities.

ETHICS STATEMENT

The experiment was approved by the Institutional Review Board of St. Anne's University Hospital, and all individuals written informed consent prior to participating.

AUTHOR CONTRIBUTIONS

KC: experimental design, behavioral data analyses, manuscript preparation. DJS: experimental design, neuroimaging data analyses, manuscript preparation. KS: recruitment and data collection, manuscript preparation. MD: clinical evaluation, manuscript preparation. RM: neuroimaging data analysis. JV: data collection. MB: experimental design, manuscript preparation.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00525/full#supplementary-material

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Altered Whole-Brain Functional Topological Organization and Cognitive Function in Type 2 Diabetes Mellitus Patients

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Type 2 diabetes mellitus (T2DM) is associated with cognitive dysfunction and may even progress to dementia. However, the underlying mechanism of altered functional topological organization and cognitive impairments remains unclear. This study explored the topological properties of functional whole brain networks in T2DM patients with graph theoretical analysis using a resting-state functional magnetic resonance imaging (rs-fMRI) technique. Thirty T2DM patients (aged 51.77 ± 1.42 years) and 30 sex-, age-, and education-matched healthy controls (HCs) (aged 48.87 ± 0.98 years) underwent resting-state functional imaging in a 3.0 T MR scanner in addition to detailed neuropsychological and laboratory tests. Then, graph theoretical network analysis was performed to explore the global and nodal topological alterations in the functional whole brain networks of the T2DM patients. Finally, correlation analyses were performed to investigate the relationship between the altered topological parameters, cognitive performances and clinical variables. Compared to HCs, we found that T2DM patients displayed worse performances in general cognitive function and several cognitive domains, including episodic memory, attention and executive function. In addition, T2DM patients showed a higher small-worldness (σ), a higher normalized clustering coefficient (γ) and a higher local efficiency (E_{loc}). Moreover, decreased nodal topological properties were mainly distributed in the occipital lobes, frontal lobes, left median cingulate and paracingulate gyri, and left amygdala, while increased nodal topological properties were mainly distributed in the right gyrus rectus, right anterior cingulate and paracingulate gyri, right posterior cingulate gyrus, bilateral caudate nucleus, bilateral cerebellum 3, bilateral cerebellum crus 1, vermis (1, 2) and vermis 3. Some disrupted nodal topological properties were correlated with cognitive performance and HbA1c levels in T2DM patients. This study shows altered functional topological organization in T2DM patients, mainly suggesting a compensation mechanism of the functional whole brain network in the relatively early stage to counteract cognitive impairments.

Keywords: type 2 diabetes mellitus, cognitive function, resting-state functional magnetic resonance imaging, topological organization, graph theoretical analysis

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INTRODUCTION

With the growth of the aging population and changes in people's living habits, the prevalence of diabetes has been increasing year by year worldwide (1, 2). Type 2 diabetes mellitus (T2DM) is the most common type, accounting for more than 90% of all diabetes. Multiple studies have shown that T2DM can increase the risk of cognitive dysfunction and may even progress to dementia, including vascular dementia and Alzheimer's disease (AD) (3–5). However, the underlying mechanism of T2DM-induced cognitive dysfunction is still unclear.

Resting-state functional magnetic resonance imaging (rs-fMRI) has become an important neuroimaging research method to understand the neurophysiological mechanisms of T2DM-induced cognitive dysfunction. Recently, many studies have focused on the functional changes of T2DM patients in a resting state. Some previous studies reported altered regional homogeneity (ReHo) values or amplitude low-frequency fluctuations (ALFF) values in the occipital lobes, temporal lobes, frontal lobes, cingulate gyrus, and cerebellum (6–8). And functional connectivity (FC) measures the similarity of the time series of two relatively remote brain regions (9). Previous studies have mainly shown impaired FC in the default mode network (DMN), ventral attention network (VAN), and dorsal attention network (DAN) (10–13). Besides, these disrupted regional brain activity and FC were associated with multiple cognitive impairments in T2DM patients, including visual processing, memory, attention, and executive function. Specifically, these methods focused only on local spontaneous brain activity using ReHo and ALFF values or concentrated their investigations within specific brain networks using seed-based approaches or independent component analysis (ICA). However, T2DM-related abnormal brain areas are extensively distributed, and cognitive dysfunction involves comprehensive interactions between different brain areas. In this context, building the functional whole brain network is necessary to comprehensively understand the underlying mechanisms of T2DM-related cognitive impairments.

The human brain is a complex network that works in a small-world network model efficiently and optimally (14). Graph theoretical analysis can effectively reflect altered topological properties of complex human brain networks. In recent years, this method has been widely used in studies of various neuropsychiatric diseases, such as AD, epilepsy and schizophrenia (15–17), while T2DM-related research was rarely reported. In the studies of functional brain network, Chen et al. (18) found that the global topological properties of the T2DM patients without cognitive dysfunction were lower than those of HCs, however, van Bussel et al. (19) revealed that the global topological properties of the T2DM patient group and the prediabetic patient group were significantly higher than those of the healthy control group and associated with lower processing speed. It can be summarized that the definite alterations of topological properties existing in the functional brain networks of T2DM patients remain unclear and the relationship between altered topological property and cognitive function is unknown. In addition, the currently studies focused only on the cerebrum networks, however, the structure and function of the cerebellum was changed in T2DM patients (7, 20). Thence, we also need to include the cerebellum to comprehensively explore the topological properties of the whole brain network.

Therefore, in the present study, we used rs-fMRI with graph theoretical analysis to explore the characteristic changes of functional whole brain network topological properties in T2DM patients. We also analyzed the correlation among the altered topological parameters, cognitive performance and related clinical variables. We hope to provide some potential imaging biomarkers of T2DM-related cognitive deficits.

MATERIALS AND METHODS

Participants

A total of 34 right-handed T2DM patients and 33 sex-, age-, and education-matched healthy controls (HCs) were recruited from the First Affiliated Hospital of Guangzhou University of Chinese Medicine. All participants received a detailed medical history interview and neurological examination. Clinical and demographic information were collected for all subjects, including biological test, blood pressure, body mass indicator (BMI), education level, alcohol consumption, smoking status, and duration of the disease (for T2DM patients only). The inclusion criteria were as follows: (1) All participants were between the ages of 40 and 65 years; (2) A standardized diagnosis of T2DM was confirmed based on medical history, medications used, fasting plasma glucose (FPG) levels ($\geq$7.0 mmol/L) or 2-h OGTT glucose levels ($\geq$11.1 mmol/L), which was in accordance with the diagnostic and classification criteria published by the American Diabetes Association (ADA) in 2014 (21); (3) HCs with FPG levels $\leq$6.1 mmol/L were included to this study. The exclusion criteria were as follows: (1) with clinically obvious complications, for example, the third or higher stages of diabetic retinopathy (based on the International Clinical Disease Severity Scale for diabetic retinopathy) (22), accompanying abnormal urinary microalbumin of nephropathy and with symptoms of peripheral neuropathy; (2)any history of severe hypoglycemia; (3) impaired glucose tolerance or impaired fasting glucose; (4) hypertension; (5) history of brain lesions such as tumor or stroke; (6) unrelated psychiatric or neurological disorder(s); (7) history of alcohol, smoke or drug abuse; (8) systemic diseases such as severe anemia, thyroid dysfunction, or acquired immune deficiency syndrome; and (9) MRI contraindications. This study was approved by the ethics committee of First Affiliated Hospital of Guangzhou University of Chinese Medicine. The current study was carried out in accordance with the principles of the Declaration of Helsinki and the approved guidelines. All participants signed informed consent before participating in the study.

Neuropsychological Test

All participants completed detailed standardized cognitive assessment, which covered multiple cognitive domains. General cognitive function was assessed by the Chinese version of the Montréal Cognitive Assessment Scale-B (MoCA-B). Episodic verbal memory was measured by the Auditory Verbal Learning

Test (AVLT). Working memory was evaluated by the Digit Span Test (DST). Attention was assessed by the Trail Making Test-A (TMT-A). Executive function was measured by the Grooved Pegboard Test. Spatial processing ability was evaluated by the Clock Drawing Test (CDT). It took approximately 40 min to finish all the tests.

Image Acquisition

For each participant, whole-brain MRI data were acquired using a 3T scanner (Signa HDxt GE Medical Systems, USA) with an 8-channel head coil. The scan time was within 1 week after medical history interview, neurological examination and biological tests, and the same day after neuropsychological tests. First, all participants underwent routine whole-brain axial T1WI (TR/TE = 2,500/24 ms), T2WI (TR/TE = 5,100/130 ms), and T2 FLAIR (TR/TE = 9,000/120 ms) to rule out intracranial organic diseases, e.g., infarction, malformation, and tumor. Resting-state fMRI data were collected using a gradient-echo EPI sequence sensitive to blood oxygen level-dependent contrast with the following parameters: TR = 2,000 ms, TE = 30 ms, flip angle = 90°, thickness = 3 mm, gap = 1 mm, FOV = 220 × 220 mm, matrix = 64 × 64, slices = 36, 185 volumes. Sagittal high-resolution T1WI whole-brain images were acquired using 3D FSPGR sequences (TR = 8.15 ms, TE = 3.17 ms, Prep Time = 450 ms, flip angle = 12°, slice thickness = 1 mm, no gap, NEX = 1, FOV = 256 × 256 mm, matrix = 256 × 256, 188 sagittal slices). Earplugs and foam pads were used to reduce equipment noise and head motion during scanning. All participants were told to lay quietly in the scanner with their eyes closed, avoiding strong ideological activities but keeping awake.

Cerebral small vascular disease, mainly including white matter hyperintensities (WMHs) and lacunar infarction, may have an impact on brain function and cognitive function (23). In this study, these changes were assessed on T2WI and T2 FLAIR images according to the age-related white matter changes (ARWMC) scale (24). Two experienced radiologists who are blinded to group status separately performed the ratings and then reached a consensus through discussion. All participants with lacunar infarcts or a rating score > 2 were excluded. Consequently, 2 T2DM patients and 1 healthy control subject were excluded from this study.

Image Preprocessing

Preprocessing of rs-fMRI data was performed with the Data Processing Assistant for rs-fMRI (DPARSF) (25) and Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) in the MATLAB version 2012a (MathWorks, Natick, MA, USA) platform. The first 10 time-points of the rs-fMRI images were removed to avoid the heterogeneity of the initial MRI signal. The 175 remaining volumes were preprocessed with the following steps: (1) slice timing, scanned image is a interleaved scan, so the slice order is [2:2:36 1:2:35] and the reference slice is 36; (2) realignment; two T2DM patients and 2 HCs were excluded from the study due to obvious head motion larger than 1.5 mm in any direction of x, y and z or 1.5° of any angular motion; (3) normalization, with the functional images coregistered to the high-resolution T1WI images; subsequently, the coregistered images were normalized into a 3 × 3 × 3 mm^3 Montreal Neurological Institute (MNI) 152 template; (4) smoothed with a 6 mm full-width half-maximum isotropic Gaussian kernel; (5) linear detrending and temporal filtering at the 0.01∼0.08 Hz band; (6) certain variables were regressed out: nuisance covariates including the white matter (WM) and the cerebrospinal fluid (CSF) signals as well as the 24 motion parameters (26); but the mean global signal was not regressed out from the data (27).

Functional Whole Brain Network Construction and Graph Analysis

Node and Edge Definitions

Network construction and analysis were performed with the GRETNA package (http://www.nitrc.org/projects/gretna), a graph theoretical network analysis toolbox for imaging connectomics. In the present study, with the automated anatomical labeling (AAL) atlas, including the cerebellum, we constructed the whole brain functional networks of all participants. First, the whole brain was parcellated into 116 different brain regions, containing 90 cerebrum areas and 26 cerebellum areas, representing the nodes of the network. Second, the functional connectivity between each pair of segmented brain regions was calculated using the Pearson correlation coefficients, representing the edges of the network. Third, a whole brain 116 × 116 correlation matrix was constructed for each participant and then translated into binarized matrices. Finally, a Fisher's r-to-z transformation was conducted to convert the individual correlation maps into z-scored maps to promote normality.

Threshold Selection and Network Analysis

In this study, whole brain functional networks were constructed based on an undirected and unweighted method. For all participants, the brain functional networks should be thresholded by a sparsity value to ensure that all resultant networks have the same number of edges and that the number of spurious edges is minimized (28, 29). However, no golden criteria are available for which sparsity value is currently the most biologically meaningful. According to previous studies (30, 31), a sparsity range of 0.05–0.5 with an interval of 0.01 was chosen, and the remaining fraction of edges was calculated in the functional network for each participant. For each sparsity threshold, eight global and nodal network parameters were computed. The global network measures included five parameters (the normalized clustering coefficient γ, the normalized characteristic path length λ, the small-worldness σ, local efficiency E_{loc} and global efficiency E_{glob}). The nodal network measures included three parameters (nodal degree, nodal efficiency and nodal betweenness). In addition, for each participant, to assess whether the network had small-world property, the network measures were normalized to comparable values from random networks ($N = 100$). Furthermore, the area under curves (AUCs), which are sensitive at detecting topological alterations of brain disorders (32), were calculated for each parameter over the entire sparsity range ($0.05 \leq Sp \leq 0.5$).

Statistical Analysis

The demographic and clinical characteristics plus neuropsychological assessment of the T2DM patients and HCs were analyzed using the IBM Statistical Package for the Social Sciences 20.0 software (IBM SPSS Inc., Chicago, IL, USA). For continuous variables, independent two-sample *t*-tests or Mann-Whitney non-parametric tests were used, according to whether they met the normal distribution and variance homogeneity. The chi-square test was used to evaluate the differences in results between the genders within the groups. With gender, age, education years, and BMI as covariates, the between-group differences in the global parameters (γ, λ, σ, E_{loc}, and E_{glob}), nodal parameters (nodal degree, nodal efficiency, and nodal betweenness) and the AUC of each parameter were compared using two-sample *t*-tests (P, 0.05) over the entire sparsity range ($0.05 \leq Sp \leq 0.5$). The Bonferroni method was applied at a *p*-value of 0.05 to correct for multiple comparisons. In addition, with the same indicators as covariates, the correlation between the altered functional network topological parameters and neuropsychological tests and clinical variables were analyzed using partial correlation analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical and Neuropsychological Results

Four T2DM patients and 3 HCs with obvious head motion or ARWMC scale rating scores > 2 were excluded, and 30 T2DM patients and 30 HCs were eventually included in the present study. The clinical and neuropsychological results of the T2DM patients and HCs are summarized in **Table 1**. The two groups were matched on age, sex, and education, and the BMI and blood lipid level were similar ($p > 0.05$), but both systolic blood pressure (SBP) ($p = 0.013$) and diastolic blood pressure (DBP) ($p = 0.035$) were higher in the T2DM patients. Compared with the HCs, the T2DM patients scored poorer on the MoCA-B ($p = 0.010$) and AVLT immediate recall tests ($p = 0.016$), spent much more time on the TMT-A ($p = 0.018$) and Grooved Pegboard Tests ($p_R = 0.009$, $p_L = 0.025$) and had no significant decreases in the other neuropsychological tests ($p > 0.05$).

TABLE 1 | Clinical and neuropsychological results of T2DM patients and HCs.

	T2DM patients ($n = 30$)	HCs ($n = 30$)	*P*-value
Clinical characteristics			
Age (years)	51.77 ± 1.42	48.87 ± 0.98	0.099
Sex (M/F)	18/12	18/12	1.000
Education (years)	10.70 ± 0.69	10.23 ± 0.61	0.614
BMI (kg/m^2)	24.82 ± 0.56	24.18 ± 0.52	0.409
SBP (mmHg)	127.20 ± 2.35	120.03 ± 1.51	0.013*
DBP (mmHg)	82.80 ± 1.67	78.70 ± 0.88	0.035*
Total cholesterol mmol/L	4.71 ± 1.78	4.27 ± 0.96	0.240
Triglyceride (mmol/L)	1.54 ± 0.92	1.48 ± 0.50	0.755
LDL cholesterol (mmol/L)	3.34 ± 1.19	2.93 ± 0.4	0.084
HDL cholesterol (mmol/L)	1.07 ± 0.29	1.15 ± 0.46	0.424
Alcohol consumption (%)			
None/Low/High	83.3/16.7/0	90.0/10.0/0	–
Smoking status (%)			
Never/Former/Current	80.0/13.3/6.7	86.7/10.0/3.3	–
Duration of diabetes (years)	5.04 ± 4.46	–	–
Fasting blood glucose (mmol/L)	8.62 ± 3.44	5.03 ± 0.48	<0.001*
2h OGTT glucose (mmol/L)	18.53 ± 5.46	–	–
HbA1C (%)	8.54 ± 2.09	–	–
Type 2 diabetes medication, yes (%)			
Oral medication	50.0	–	–
Insulin medication	16.7	–	–
Insulin and oral medication	20.0	–	–
None(newly diagnosed)	13.3	–	–
Cognitive scores			
MoCA-B	25.23 ± 0.66	27.23 ± 0.34	0.010*
AVLT immediate recall	18.00 ± 0.80	21.17 ± 0.99	0.016*
AVLT short-term recall (5 min)	7.03 ± 0.43	7.97 ± 0.38	0.108
AVLT long-term delayed recall (20 min)	7.60 ± 0.52	7.70 ± 0.40	0.839
AVLT recognition	10.23 ± 0.43	11.00 ± 0.27	0.139
TMT-A	67.17 ± 5.94	50.57 ± 3.19	0.018*
Grooved Pegboard (R)	92.07 ± 5.63	75.30 ± 2.31	0.009*
Grooved Pegboard (L)	96.83 ± 5.30	83.57 ± 2.05	0.025*
DST	11.87 ± 0.39	12.73 ± 0.46	0.154
CDT	2.63 ± 0.11	2.77 ± 0.08	0.335

*Data are mean ± SD. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MoCA-B, Montreal cognitive assessment-B; AVLT, Auditory verbal learning test; TMT-A, Trail making test-A; DST, digit span test; CDT, Clock drawing test. *P < 0.05, which was considered statistically significant.*

Small-World Properties of Resting-State Functional Networks

Compared to random networks, the functional brain networks of the two groups had relatively higher normalized clustering coefficients ($\gamma > 1$), similar characteristic path lengths ($\lambda \approx 1$), and small-worldness σ ($\sigma = \gamma/\lambda > 1$), that is, demonstrated small-world property (**Figures 1A–C**).

Altered Small-World Property and Network Efficiency in T2DM Patients

Compared to HCs, T2DM patients showed increased γ values over the entire sparsity range ($0.05 \leq Sp \leq 0.5$), increased σ and E_{loc} values for a range of sparsity values (σ: $0.13 \leq Sp \leq 0.5$ and E_{loc}: $0.09 \leq Sp \leq 0.31$) (**Figures 1A,C,D**). Moreover, T2DM patients showed the AUC values of γ ($p = 0.019$), σ ($p = 0.032$), and E_{loc} ($p = 0.034$) were significantly higher than HCs (**Figure 2**). However, λ and E_{glob} values were similar between T2DM patients and HCs ($p > 0.05$) (**Figures 1B,E**, **2**).

Altered Nodal Topological Metrics in T2DM Patients

We identified 26 brain regions with altered nodal parameters between the T2DM patients and the HCs in at least one of the three nodal characteristics, which are reported in **Table 2**. Compared to the HCs, the T2DM patients showed decreased nodal parameters in frontal lobes [right precentral

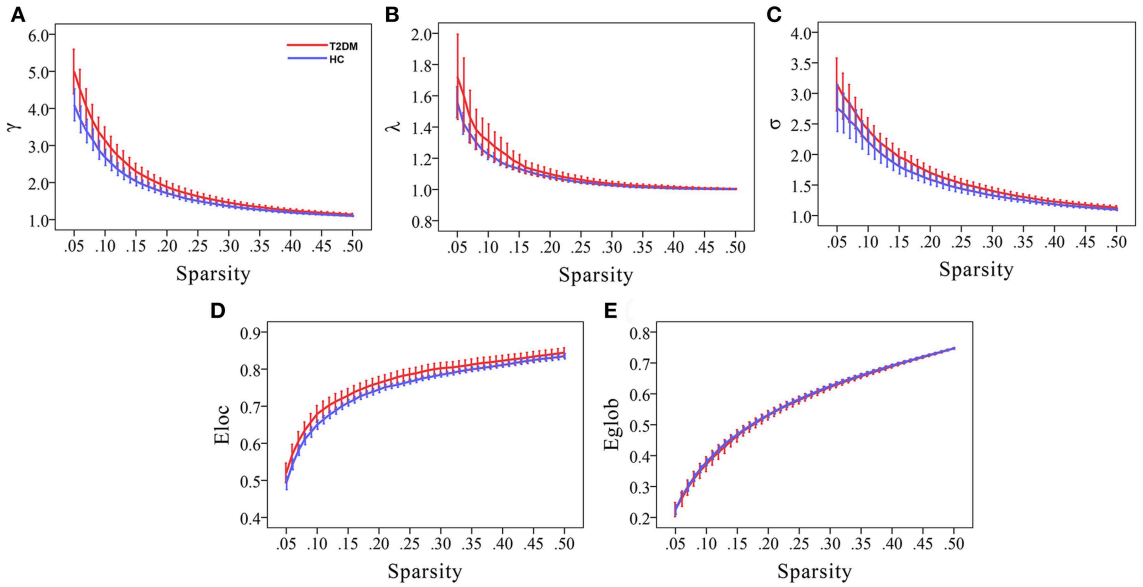

FIGURE 1 | Small-world property and network efficiency measures of the whole brain network over the defined wide range of sparsity values of T2DM patients and healthy controls. Compared to random networks, graphs display that both the two groups had relatively higher normalized clustering coefficients ($\gamma > 1$), similar normalized characteristic path lengths ($\lambda \approx 1$), and small-worldness σ ($\sigma = \gamma/\lambda$) > 1, that is, demonstrated small-world property **(A–C)**. Moreover, T2DM patients had higher local efficiency and similar global efficiency than HCs **(D,E)**.

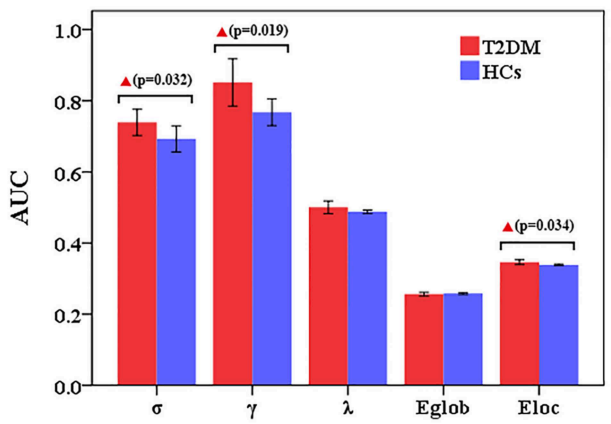

FIGURE 2 | Altered small-world property and network efficiency measures of the whole brain network over the defined wide range of sparsity values between T2DM patients and healthy controls. Compared to HCs, T2DM patients showed the AUC values of γ ($p = 0.019$), σ ($p = 0.032$), and Eloc ($p = 0.034$) were significantly higher than HCs. However, λ and Eglob values were similar between T2DM patients and HCs.

gyrus (PreCG.R), right supplementary motor area (SMA.R), left superior frontal gyrus, dorsolateral (SFGdor.L), left superior frontal gyrus, medial (SFGmed.L)], occipital lobes [right cuneus (CUN.R), bilateral lingual gyrus (LING.L&R), bilateral superior occipital gyrus (SOG.L&R) and middle occipital gyrus (MOG.L&R)], left amygdala (AMYG.L), left median cingulate and paracingulate gyri (DCG.L), and left supramarginal gyrus (SMG.L). However, T2DM patients exhibited increased nodal parameters in the right gyrus rectus (REC.R), right anterior cingulate and paracingulate gyri (ACG.R), right posterior cingulate gyrus (PCG.R), left angular gyrus (ANG.L), bilateral caudate nucleus (CAU.L&R), bilateral cerebellum 3 (CRBL3.L&R), bilateral cerebellum crus 1 (CRBLCrus1.L&R), vermis (1, 2) and vermis 3 compared to HCs. Most (14/26) brain regions demonstrated decreased nodal parameters in T2DM patients, with the remaining 12 brain regions showing increased nodal parameters.

Correlation Analyses Among Altered Network Parameters, Cognitive Function and Clinical Variables

In T2DM patients, MoCA-B scores were positively correlated with the nodal degree ($r = 0.400$, $p = 0.043$) and nodal efficiency ($r = 0.452$, $p = 0.021$) of the REC.R. AVLT immediate recall scores were positively correlated with the nodal betweenness of the AMYG.L ($r = 0.457$, $p = 0.019$), and AVLT short-term recall scores were positively correlated with the nodal degree of the CRBL3.R ($r = 0.431$, $p = 0.028$). Both the Grooved Pegboard-R ($r = -0.461$, $p = 0.018$) and Grooved Pegboard-L ($r = -0.436$, $p = 0.026$) were negatively correlated with the nodal betweenness of the MOG.R. HbA1c was negatively correlated with the nodal betweenness of the PCG.R ($r = -0.388$, $p = 0.034$) and AVLT immediate recall scores ($r = -0.458$, $p = 0.019$). Correlation analyses were illustrated in **Figure 3**. No relationship was found in altered global network parameters.

TABLE 2 | Brain regions with altered nodal parameters in T2DM patients.

AAL no.	Brain Regions		*p*-values		
	Regions	Abbreviation	Nodal degree	Nodal efficiency	Nodal betweenness
T2DM<HC(14/26)					
2	Right precentral gyrus	PreCG.R	0.052	**0.034**	**0.036**
3	Left superior frontal gyrus (dorsolateral)	SFGdor.L	0.519	0.196	**0.005**
20	Right supplementary motor area	SMA.R	0.141	0.156	**0.044**
23	Left superior frontal gyrus (medial)	SFGmed.L	0.335	0.183	**0.012**
33	Left median cingulate and paracingulate gyri	DCG.L	0.059	**0.037**	0.652
41	Left amygdala	AMYG.L	0.499	0.385	**0.026**
46	Right cuneus	CUN.R	0.054	**0.039**	0.652
47	Left lingual gyrus	LING.L	**0.008**	**0.009**	0.340
48	Right lingual gyrus	LING.R	**0.008**	**0.012**	0.531
49	Left superior occipital gyrus	SOG.L	**0.004**	**0.010**	0.135
50	Right superior occipital gyrus	SOG.R	**0.016**	**0.017**	0.656
51	Left middle occipital gyrus	MOG.L	0.058	**0.045**	**0.010**
52	Right middle occipital gyrus	MOG.R	**0.039**	**0.015**	**0.047**
63	Left supramarginal gyrus	SMG.L	0.058	**0.037**	**0.024**
T2DM>HC(12/26)					
28	Right gyrus rectus	REC.R	**0.048**	**0.034**	0.252
32	Right anterior cingulate and paracingulate gyri	ACG.R	0.930	0.597	**0.040**
36	Right posterior cingulate gyrus	PCG.R	0.488	0.903	**0.033**
65	Left angular gyrus	ANG.L	0.865	0.552	**0.040**
71	Left caudate nucleus	CAU.L	**0.001**	**0.004**	**0.005**
72	Right caudate nucleus	CAU.R	**0.030**	**0.030**	0.084
91	Left cerebellum crus1	CRBLCrus1.L	0.150	0.374	**0.049**
92	Right cerebellum crus1	CRBLCrus1.R	0.182	0.504	**0.025**
95	Left cerebellum 3	CRBL3.L	**0.010**	**0.011**	0.532
96	Right cerebellum 3	CRBL3.R	**0.004**	**0.001**	0.208
109	Vermis (1, 2)	Vermis(1, 2)	**0.015**	0.140	0.616
110	Vermis 3	Vermis 3	**0.003**	0.141	**0.023**

AAL No., number of automated anatomical labeling. Note: Brain regions were considered abnormal in T2DM patients if they showed $p < 0.05$ compared to HCs in at least one of the three nodal parameters and boldface p-values were statistically significant.

DISCUSSION

In this cross-sectional study, we focused on the topological organization of rs-fMRI whole brain network of middle-aged T2DM patients without obvious complications using graph-based theoretical approaches. The results displayed that both the two groups exhibited small-world organization of their functional networks, but compared to HCs, T2DM patients showed (1) a higher normalized clustering coefficient (γ), a higher small-worldness (σ) and a higher local efficiency (E_{loc}); (2) both decreased and increased nodal network parameters; (3) altered nodal network parameters of some brain regions were related to cognitive impairments and HbA1c. These findings provide new insight into the underlying functional neuropathological effects of T2DM-related cognitive impairments.

Increased Global Network Measures

The small-world network, with a similar characteristic shortest path length and a higher clustering coefficient compared to the random network, is a highly integrated and optimized network model that can maximize efficiency and minimize information processing. Small-world networks were found not only in real-world networks, for example, social, traffic, and genetic networks, but also in functional, structural, and EEG human brain networks. In this study, the functional whole brain networks of both T2DM patients and HCs exhibited small-world organization, which was consistent with previous studies (18, 19, 32, 33).

As far as we know, normal human brain networks that combine a high σ, a high γ, and a high E_{loc} indicate a highly integrated and optimized network, a high local effectiveness in processing information and a high fault tolerance of the network. Our investigation showed this combination in T2DM patients, implying that the whole brain networks were better organized than those in HCs. The result seems unreasonable and converse because the networks of T2DM patients should be less, instead of better, organized. However, in the research of the rs-fMRI network among T2DM patients, prediabetes patients and healthy controls, van Bussel et al. (19) found

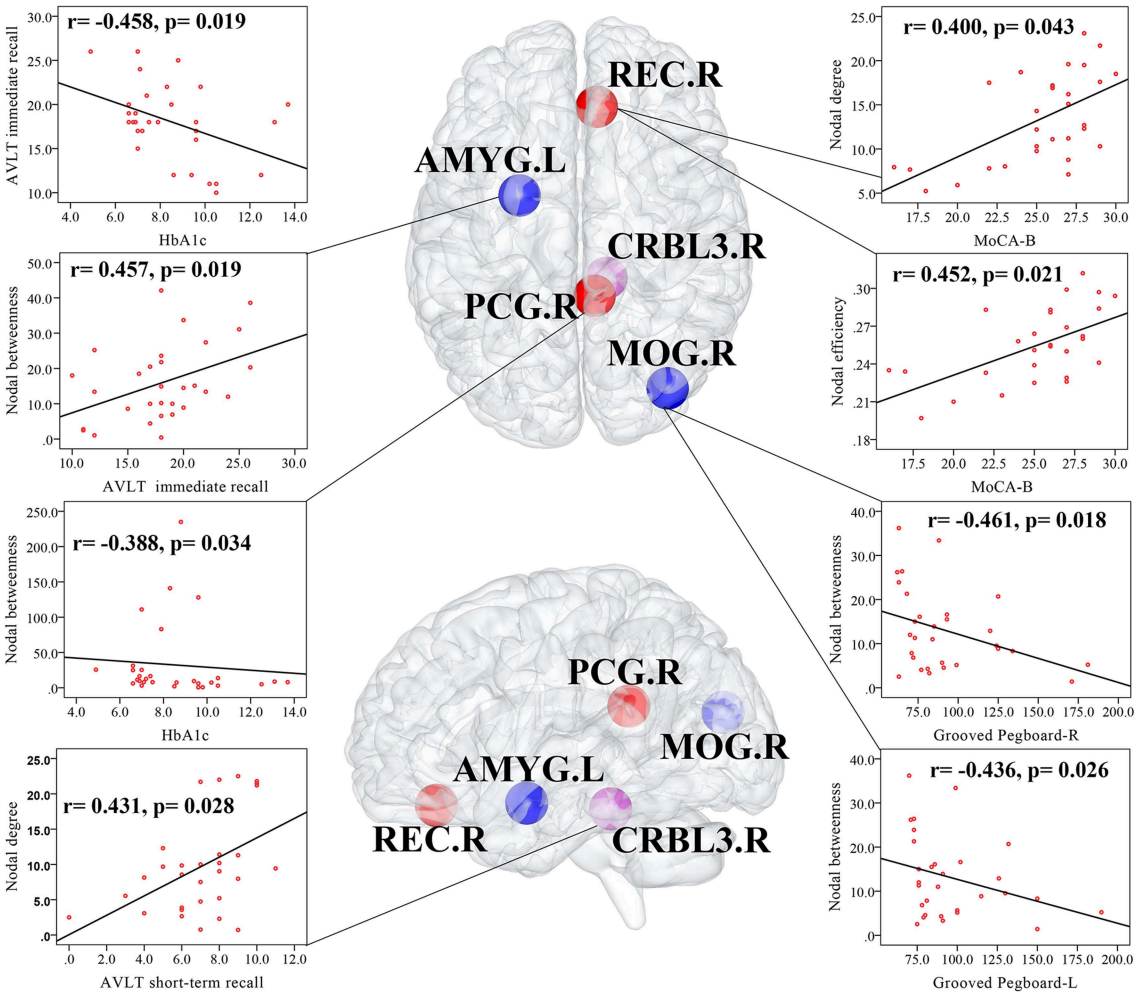

FIGURE 3 | Correlations among altered network measures, cognitive function, and HbA1c in T2DM patients. Scatter plot displayed the relationship between the altered network parameters and clinical variables in T2DM patients. The blue ball represented the decreased nodal parameters and the red ball and purple ball represented the increased nodal parameters. MOG.R, right middle occipital gyrus; AMYG.L, left amygdala; REC.R, right gyrus rectus; PCG.R, right posterior cingulate gyrus; right cerebellum 3, CRBL3.R.

results similar to our study. They held the view that before the appearance of clinically manifested cognitive decrements, the brain functional network may have already reorganized as a compensatory mechanism to counterwork the slight cognitive decrements. Once the functional reorganization fails, there will be a disrupted functional network and clinically manifested cognitive decrements will be discovered in T2DM patients. MoCA-B is widely used to assess general cognitive function and is more sensitive than MMSE. The mean MoCA-B score was 25.23 ± 0.66 in the T2DM patients in our study, which was slightly lower than the normal score 26, suggesting a stage of slight cognitive decrements. Besides, the included T2DM patients are middle-aged, with a short diabetes duration and well-controlled glucose levels, and without obviously complications, thus they may be relatively "healthy" patients. Therefore, the better organized whole brain networks in the T2DM patients of our study also supported the compensatory mechanism put forward by van Bussel et al. However, Chen et al. (18) showed longer path length and lower global efficiency but similar clustering coefficient and local efficiency in T2DM patients without mild cognitive impairment (MCI), indicating a less rather than better organized functional network, which is not consistent with our findings. These differences may be attributed to the severity of the disease condition or the sensitivity of the different neuropsychological tests and need to be discussed through longitudinal, large sample, long-term investigations in the future. Moreover, disrupted structural networks have already been reported via graph theoretical network analysis in T2DM patients (32, 33), but the relationship between the brain structural network and the functional network is still unknown. We believe that it is meaningful to combine structural networks with functional networks using theoretical network analysis to explore the underlying mechanism of T2DM-related cognitive function in the future.

Decreased Nodal Network Measures

Nodal network parameters (nodal degree, nodal efficiency and nodal betweenness) can detect the activity, importance and influence of a region in network communication. In our study, reduced nodal parameters were observed in the occipital lobes, frontal lobes, left median cingulate and paracingulate gyri, left amygdalaleft and supramarginal gyrus. And the decreased nodal parameters of occipital lobes existed in CUN.R, bilateral LING, SOG, and MOG. Recently, a study found that the degree centrality of the LING was significantly reduced in T2DM patients and the connectivity within the LING-related visual network was diffusely decreased (34). Moreover, they found positive correlations of the occipital connectivity with visual memory and executive performance. In addition, in the earlier studies, T2DM patients showed not only decreased volume and brain metabolites (35, 36) but also decreased ReHo and ALFF values of the occipital lobes, especially in CUN, LING, SOG, MOG and calcarine gyrus (CAL) (6, 8, 37). In our study, the nodal degree of the MOG.R was negatively correlated with the consumed time of the Grooved Pegboard Test (a scale reflecting execution function), suggesting that a decreased nodal degree of the MOG.R may be attributed to reduced performance in executive function.

The cingulate gyrus is the core node in the DMN and acts as a transportation hub during information transmission processing and participates in various cognitive functions. To the best of our knowledge, only one study showed that the increased degree centrality of the dorsal anterior cingulate cortex (dACC) and the increased connectivity of the dACC was related to higher FPG levels and better TMT-B performance in T2DM patients (34). But impaired functional activity of DMN has been widely reported in previous studies using ReHo, ALFF, seed-based approaches or independent component analysis (12, 38, 39). Our study found that the nodal parameters in the DCG.L and SMG.L were reduced, while the nodal parameters in the ACG.R and PCG.R were increased. These findings may be interpreted as the fact that the left hemisphere of the recruited right-handed participants are more active than the right hemisphere and more sensitive to pathological changes caused by hyperglycemia, thus, compensatory increases of the right cingulate gyrus will be made to maintain the brain function activities of the whole brain. Furthermore, the nodal betweenness of the PCG.R was negatively correlated with HbA1c, suggesting that controlling and monitoring the HbA1c value is of great significance for the development of diabetic encephalopathy.

The frontal lobe is the latest and most advanced part of brain development. It is widely accepted that the frontal lobes, especially prefrontal lobes, are primarily responsible for high-order cognitive control (40, 41), and appear to be vulnerable regions in T2DM patients by using functional connectivity and graph theoretical network analysis (13, 19, 32). In this study, as shown in **Table 2**, several frontal lobes (PreCG.R, SMA.R, SFGdor.L, and SFGmed.L) showed decreased nodal parameters, while the REC.R showed increased nodal parameters. In addition, increased nodal degree and nodal efficiency of the REC.R were related to higher MoCA-B scores. These results suggest that disrupted frontal topological properties may further explain the damaged neural mechanism and declined cognitive function in T2DM patients. The AMYG is located in the medial temporal lobe and is mainly involved in mood and memory. The AMYG.L performed decreased nodal betweenness and was related to worse performance in the AVLT immediate recall test, suggesting that its ability to participate in network information transmission was reduced and may partially explain the reason for memory loss in T2DM patients. Recently, Xia et al. (42) reported that T2DM patients may be accompanied by depressive mood, and depressed T2DM patients showed decreased AMYG FC when compared to non-depressed T2DM patients. However, our study did not assess depression-related scales, and this needs to be further discussed in future studies.

Increased Nodal Network Measures

Finally, to the best of our knowledge, this study is the first to explore the topological properties of whole-brain (including cerebellum) functional networks using graph theoretical analysis in T2DM patients. In the previous studies of resting state functional MRI, increased ReHo or ALFF values and functional connectivity of the cerebellum posterior lobe and cerebellum culmen were reported in T2DM patients (7, 8, 43). They hold the view that cerebellum, especially the cerebellum posterior lobe, may play a role of compensation. And this study demonstrated increased nodal parameters in the bilateral cerebellum 3, bilateral cerebellum crus 1, vermis (1, 2) and vermis 3, which was partly consistent with the previous studies. Moreover, in the previous studies of structural MRI, decreased FA values of vermis (44) and increased MD values of bilateral cerebellum anterior and posterior lobes (45) were reported, and some decreased connections in cerebellar and cerebro-cerebellar circuit were found (20). These studies displayed that the cerebellum was both damaged in function and structure, but there was no report about the definite relationship between cerebellum and cognitive function in T2DM patients. The cerebellum not only plays an important role in motor control and coordination but also relates to some advanced cognitive functions, such as language, emotional modulation, episodic and working memory (46–48). In the present study, the nodal degree of the right cerebellum 3 was positively correlated with the AVLT short-term delayed recall score, suggesting a close relationship between the cerebellum and memory. Therefore, we speculate that in the relatively early stage, the elevated brain functional activity of the cerebellum, especially the cerebellum posterior lobe, can recruit more nerve resources as a compensation mechanism to slow the process of cognitive decline. This may also explain why the local efficiency of T2DM patients is higher than that of HCs from another expect, which may be due to the compensation mechanism of the increased nodal properties in the these brain regions mentioned above.

LIMITATIONS

This study had some limitations. First, it was a cross-sectional study that did not assess the progression of functional network changes and had a relatively small sample size. Second, the medication of T2DM patients was not completely identical,

so medication confounding effects may exist. Therefore, the effect of medication needs to be investigated in future studies. Third, previous studies reported that T2DM patients may have depression, but our study did not assess the patient's mood state with a detailed depression scale. Moreover, according to the presence depression, we can divide these T2DM patients into different subgroups and further explore the differences between them. Finally, we only explored the relationship between the brain functional network and cognitive performance in T2DM. The incorporation of a structural network allowed us to examine whether the functional changes underlying cognitive dysfunction in T2DM are associated with structural network alterations. Further studies that combine multimodal imaging techniques will be helpful to interpret this issue.

CONCLUSION

In summary, this study displayed disrupted functional networks in middle-aged T2DM patients with mild cognitive impairments, demonstrating a more efficient global topological organization and showing both decreased and increased nodal parameters. This may suggest a compensation mechanism for cognitive decline in terms of functional reorganization of the whole brain networks. Furthermore, the study demonstrated that graph theoretical network analysis provided novel insight and the results may serve as potential imaging biomarkers for subtle whole brain alterations of T2DM-related cognitive decline.

ETHICS STATEMENT

This study was approved by the ethics committee of First Affiliated Hospital of Guangzhou University of Chinese Medicine. The current study was carried out in accordance with the principles of the Declaration of Helsinki and the approved guidelines. All participants signed informed consent before participating in the study.

AUTHOR CONTRIBUTIONS

CQ carried out the data collection, analysis and interpretation, and drafted the initial article. YL, XT, HZ, JY, YfL, and YZ participated in the data collection and interpretation. XL, HL, CZ and SQ contributed to the conception and design of the study, interpretation of data, and manuscript revision. All authors read the final manuscript and approved it for publication.

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REVIEW
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Crosstalk Between the Gut Microbiota and the Brain: An Update on Neuroimaging Findings

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An increasing amount of evidence suggests that bidirectional communication between the gut microbiome and the central nervous system (CNS), which is also known as the microbiota-gut-brain axis, plays a key role in the development and function of the brain. For example, alterations or perturbations of the gut microbiota (GM) are associated with neurodevelopmental, neurodegenerative, and psychiatric disorders and modulation of the microbiota-gut-brain axis by probiotics, pre-biotics, and/or diet induces preventative and therapeutic effects. The current interpretation of the mechanisms underlying this relationship are mainly based on, but not limited to, parallel CNS, endocrine, and immune-related molecular pathways that interact with each other. Although many studies have revealed the peripheral aspects of this axis, there is a paucity of data on how structural and functional changes in the brain correspond with gut microbiotic states *in vivo*. However, modern neuroimaging techniques and other imaging modalities have been increasingly applied to study the structure, function, and molecular aspects of brain activity in living healthy human and patient populations, which has resulted in an increased understanding of the microbiota-gut-brain axis. The present review focuses on recent studies of healthy individuals and patients with diverse neurological disorders that employed a combination of advanced neuroimaging techniques and gut microbiome analyses. First, the technical information of these imaging modalities will be briefly described and then the included studies will provide primary evidence showing that the human GM profile is significantly associated with brain microstructure, intrinsic activities, and functional connectivity (FC) as well as cognitive function and mood.

Keywords: gut microbiota, microbiota-gut-brain axis, neuroimaging, mutimodal, mutual communication

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INTRODUCTION: THE MICROBIOME-GUT-BRAIN AXIS

Bidirectional interactions between the brain and gut and their relationships with a third component, the gut microbiome, have received increasing attention in recent years (1–3). Emotional and psychosocial factors can trigger gastrointestinal symptoms such as heartburn, indigestion, acid reflux, bloating, pain, constipation, and diarrhea (4). Conversely, a series of pre-clinical investigations has shown that dysbiosis and/or alterations of the gut microbiota (GM) are implicated in the pathogeneses and pathophysiologies of intestinal diseases, such as

inflammatory bowel disease (IBD), as well as neurological disorders, and psychiatric conditions, including anxiety, depression, autism spectrum disorder (ASD), multiple sclerosis, Alzheimer's disease (AD), and Parkinson's disease (PD). However, clinical evidence supporting such interactions in humans remains relatively scarce (5–12).

Although a variety of mechanisms have been proposed to support interactions within the microbiome-gut-brain axis (MGBA) (13–16), the GM primarily communicates with the central nervous system (CNS) via neural, immune-related, endocrine, and metabolic signaling pathways (17). Chemically, the GM and brain communicate with each other using hormones, such as corticotrophin-releasing hormone (CRH) in the hypothalamic-pituitary-adrenal (HPA) axis, neurotransmitters, such as serotonin (5-HT), dopamine, and γ-aminobutyric acid (GABA), neuropeptides, and short-chain fatty acids (SCFAs) (14, 18–20).

Additionally, novel advanced methods have facilitated current understanding of these complex interactions *in vivo* and revealed the peripheral aspects of the MGBA. For example, 16s rRNA gene sequence analyses and/or high-throughput sequencing can demonstrate GM composition in terms of diversity and abundance (21, 22) and provide qualitative and quantitative information about bacterial species and changes (23). Likewise, biochemistric and molecular biological methods can identify metabolic, immunological, and endocrine molecules from different body fluids and tissues. Meanwhile, advanced neuroimaging methods have emerged as an effective tool for understanding the structure, function, and molecular aspects of the brain, which is the central component of the MGBA. Using such techniques, imaging parameters can also aid *in vivo* explorations of the potential associations between the microstructural patterns or functional conditions in the brain and particular dysbiotic states in the gut (24).

The present review assessed studies (see **Table 1**) of healthy individuals and patients with diverse neurological disorders that combined advanced neuroimaging techniques with GM analyses. First, the technical information of various neuroimaging modalities will be presented and then the published results of brain imaging and GM analyses as well as their correlations in healthy subjects and patient populations will be discussed.

MULTIMODAL NEUROIMAGING METHODS

Magnetic resonance imaging (MRI) is a widely used non-invasive technique capable of reflecting structural, functional, and metabolic brain properties. Additionally, this technique is readily translated between preclinical and clinical settings. In this section, the primary MRI sequences that have been utilized to study the relationship between the GM and the human brain will be discussed.

Structural MRI Techniques

Typically, studies will assess gray matter structures in the brain in terms of global or regional cortical volume and thickness. With the development of novel analysis methods, several studies have demonstrated structural differences in the brain among different patient populations. For example, voxel-based morphometry (VBM) (31) allows for automated, quantitative, and objective evaluations of gray matter volume across the brain whereas diffusion tensor imaging (DTI), which is derived from diffusion-weighted imaging (DWI), is well-suited for visualizing the microstructural details of white matter *in vivo*. DTI has several metrics that quantify the degree and direction of water diffusion. Fractional anisotropy (FA), which is the most commonly assessed metric, measures the directional coherence of water diffusion within tissues and reflects the degree of structural integrity and the myelination of white matter. In addition to basic 3D visualization methods, fiber tracking has been used to delineate specific white matter tracts for quantitative analyses in various groups, including pediatric subjects, elderly subjects, and patients with schizophrenia, brain tumors, AD, or other disorders (32, 33).

Preclinical evidence has also demonstrated that the GM plays a critical role in the development and function of CNS tissues via different metabolic or immune-related signaling pathways. From a structural point of view, region-specific changes in the brains of GM-free (GF) animals have been associated with specific GM metabolites. For example, the levels of brain-derived neurotrophic factor (BDNF), which is a key regulator of synaptic plasticity and neurogenesis in the brain, are reduced in the cortex and hippocampus of GF mice (34). Additionally, synaptophysin, which is a marker of synaptogenesis, and PSD-95, which is a marker of mature excitatory synapses, are lower in the striatum of GF animals compared to specific pathogen-free animals (35). Butyrate, which is an important SCFA, is associated with the increased expression of occludin, which is a tight junction protein, in the frontal cortex and hippocampus (36). The GM is also a critical promoter of microglial maintenance in the CNS during sensitive developmental periods. Furthermore, recent increases in the specificity of neuroimaging techniques have allowed for the visualization of different tissue sub-compartments (e.g., glia vs. neurons, the soma vs. dendrites, axon diameter vs. myelin thickness or axonal density) and created the possibility of unmasking subtle microstructural changes *in vivo* (22).

Importantly, an *ex-vivo* DTI study in rats conducted by Ong (37) demonstrated that diet-specific GM populations are associated with differences in brain microstructures, particularly white matter integrity. Neuroimaging techniques have also been used to investigate the central mechanisms associated with IBS in human patients. An analysis of cortical thickness that employed structural MRI with VBM showed that female patients with IBS exhibit reduced cortical thickness in the anterior insular cortex but increased cortical thickness/gray matter volume in the post-central gyrus. However, the findings of DTI studies are inconsistent in terms of changes in FA (38).

Functional Neuroimaging Techniques

In terms of functional changes, functional MRI (fMRI) analyses using blood oxygenation level-dependent (BOLD) signals remain one of the most widely used methods for mapping and studying the neural basis of human cognition in both healthy and dysfunctional brains (39). Conventionally, alterations in neural activities can be recorded by asking the subject to perform a

TABLE 1 | Crosstalk between the GM and human brain function.

Subjects	Intervention	Measures	Results				References
			Neuroimaging results	GM results	Correlation	Other	
Healthy women	FMPP for 4w (FMPP group, $n = 12$; non-FMPP group, $n = 12$; no intervention, $n = 13$)	Task-based fMRI and rs-fMRI; GM (fecal samples)	Emotional attention task based-fMRI: sensory brain network connection strength and decreases in insular and somatosensory cortical BOLD activity↓ in the FMPP group rs-fMRI: PAG was negatively correlated with sensory/affective regions and positively correlated with cortical regulatory regions (medial and dorsolateral prefrontal cortices) in FMPP group	No significant changes in fecal microbiota composition	Four-week intake of an FMPP by healthy women affected activity in brain regions that control the central processing of emotion and sensation	/	(25)
Obese and non-obese subjects	No intervention (20 obese and 19 non-obese subjects)	MRI; DTI; FLAIR; R2*; GM (fecal samples); cognitive tests	See the correlation column	16S bacterial gene pyrosequencing: fecal sample bacterial biodiversity↓ in obese men	Fecal microbiota diversity was negatively correlated with R2* signals in the hypothalamus, hippocampus, and caudate nucleus. The abundance of Actinobacteria was positively associated with FA in the amygdala and thalamus but negatively correlated with the R2* signal in the hypothalamus	The relative abundance of the Actinobacteria Phylum was positively associated with cognitive tests related to speed, attention, and cognitive flexibility	(26)
Elderly outpatients with and without cirrhosis	No intervention Group type 1: 39 cirrhotic and 37 non-cirrhotic patients; Group type 2: unimpaired cognition ($n = 23$), amnestic-type ($n = 25$), and amnestic/non-amnestic type ($n = 28$).	Multi-modal MRI (fMRI go/no-go task, volumetry, and MRS); inflammatory cytokines; GM (fecal samples); neuropsychological tests	No significant fMRI differences in brain volumes between cirrhotic and non-cirrhotic subjects. Amnestic/non-amnestic type: activation in the central opercular cortex, post-central gyrus, and superior parietal lobule during inhibition↑. Amnestic-type type: white matter, gray matter, and total brain volumes↓, hippocampal and left thalamic volumes↓ Cirrhotic subjects: mi/Cr and NAA/Cr ratios↓ and Glx/Cr ratio↑. Amnestic/non-amnestic type: mi/Cr and Glx/Cr ratios↓	Cirrhotic subjects: *Lactobacillales*↑ and *Synergisticeae*, and *Peptococcaceae*↓. Cognitively impaired groups: decreased *Subdoligranulum*, *Oscillibacte*, and *Porphyromona*daceae and *Prevotellaceae*↓ and *Bacteroides*↑ Unimpaired group: increased *Fecalibacterium* and *Butyricicoccus*	Regardless of the presence of cirrhosis, beneficial taxa (*Lactobacillales*, *Ruminococcaceae*, and *Lachnospiraceae*) were positively linked with cognition while pathogenic taxa (*Enterobacteriaceae*) were negatively linked with cognition	Serum levels of IL-6/endotoxin↑	(27)

(Continued)

TABLE 1 | Continued

Subjects	Intervention	Measures	Results				References
			Neuroimaging results	GM results	Correlation	Other	
Cirrhosis patients with/without prior HE	No intervention (Cirrhotic without prior HE, $n = 62$; cirrhotic with prior HE, $n = 85$; controls, $n = 40$)	MRS, DTI, Systemic inflammatory assessment, GM (fecal samples); cognitive testing	MRS: Cirrhotic patients with HE: Glx↑↑ mi↓↓; Cho↓↓; Cirrhotics: Glx↑ mi↓; DTI: Cirrhotics with HE: spherical isotropy↑, FA↓	Cirrhotic patients with HE: *Staphylococcaceae*↑, *Enterococcaceae*↑, *Porphyromonadaceae*↑, and *Lactobacillaceae*↑; autochthonous bacterial families (*Lachospiraceae*↓, *Ruminococcaeae*↓, and *Clostridiales* XIV↓	Autochthonous taxa were negatively correlated with hyperammonemia-associated astrocytic MRS changes while *Enterobacteriaceae* were positively correlated with hyperammonemia-associated astrocytic MRS changes (high Glx levels and low mi and Cho levels). *Porphyromonadaceae* were correlated with neuronal changes on DTI without being linked to ammonia	Cirrhotic patients with prior HE had significantly more advanced cirrhosis, more severe and higher levels of inflammatory markers and cognitive impairments compared to cirrhotic patients without HE	(28)
IBS patients with anxiety and depression	Probiotic: *Bifidobacterium longum* NCC3001 for 6 w (BL, $n = 22$; placebo, $n = 22$)	Task-based fMRI (fearful face backward masking paradigm); fecal microbiota; urine metabolome profiles; serum inflammatory markers; neurotransmitter and neurotrophin levels	BL reduced responses to negative emotional stimuli in multiple brain areas including the amygdala and fronto-limbic regions	No major changes in fecal microbiota composition after intervention	Reduced amygdala activity was correlated with decreases in depression scores	Depression scores↓; IBS symptoms improved; urine levels of methylamines and aromatic amino acid metabolites↓	(29)
Healthy women (*Bacteroides*-high group vs. *Prevotella*-high group)	No intervention	Emotion-induced task-based fMRI; structural MRI (DTI, T1)	*Prevotella* group: right hippocampal activity↓ when viewing negative valence images. *Bacteroides*-high group: white matter connectivity↓, cerebellum, frontal region, and hippocampal volumes↑, and nucleus accumbal volume↓	Subjects were divided into *Bacteroides*-high group and *Prevotella*-high group based on fecal microbiota analysis	/		(30)
Obese and non-obese subjects	Diet counseling (18 obese and 17 non-obese subjects)	MR relaxometry R2*; GM (fecal samples); Neuropsychological tests; plasma β-amyloid (1–24, 31–48) levels	MR R2* relaxometry increased mainly in the pallidum, putamen, thalamus, and hippocampus in both groups over a 2-year period	A variety of gut microbiome changes in RA over a 2-year period	Shifts in *Gemmatimonadetes*, *Bacteroidetes*, *Proteobacteria*, *Caldiserica*, *Candidatus*, *Saccharibacteria*, *Tenericutes*, *Thermodesulfobacteria*, and *Chlorobi* RA were associated with increased percentages of R2* in the striatum, superficial amygdala, and hippocampus. Shifts in the phyla *Fibrobacteres*, *Synergistetes*, and *Tenericutes* RA were reciprocally associated with right hippocampal R2*.	Circulating β-amyloid Ab42 levels were positively associated with changes in visuospatial constructional ability and immediate memory but negatively associated with increases in R2*	(49)

(Continued)

TABLE 1 | Continued

Subjects	Intervention	Measures	Results				References
			Neuroimaging results	GM results	Correlation	Other	
Healthy volunteers	Probiotic (Ecologic825, nine bacterial strains) for 4w (probiotic, $n = 15$; placebo, $n = 15$; no intervention, $n = 15$)	Task-based fMRI (emotional decision-making and emotional recognition memory); DTI; neuropsychological tests	Altered brain activation in the cingulum, precuneus, inferior parietal lobule, thalamus, and parahippocampal gyrus in the ED task and cerebellar activity in the ER task	No major changes in general fecal microbial diversity or evenness; *Bacteroides sp.*↑, *Alistipe sp.*↑, and the nicotinate and nicotinamide metabolic pathway of fecal microbiota↓	Probiotic ingestion improved emotional attention and memory performance, which was accompanied by changes in activity in corresponding brain regions	Self-reported behavioral measures of positive affect, cognitive reactivity, and memory performance improved	(50)
Healthy volunteers	Probiotic (Ecologic825, nine bacterial strains) for 4w (probiotic, $n = 15$; placebo, $n = 15$; no intervention, $n = 15$)	Rs-fMRI; diffusion MRI	FC in MFGN (in frontal pole and frontal medial cortex) and in DMN (in frontal lobe)↓, FC in SN (in cingulate gyrus and precuneus cortex)↑. No significant changes in structural connectivity (FA/MD)	Same as above [Bagga et al. (50)]	Probiotic intervention was -associated with -changes in FC but not structural connectivity		(51)
High-risk (HR) and ultra-high risk (UHR) subjects for schizophrenia	No intervention (high-risk group, $n = 81$; ultra-high risk group, $n = 19$; healthy controls, $n = 69$)	MRS; GM (fecal samples).	Ultra-high risk group: Cho levels in anterior cingulate cortex↑	Ultra-high risk group: at order level; *Clostridiales*, *Lactobacillales*, and *Bacteroidales*↑; at general level, *Prevotella* and *Lactobacillus*↑; synthesis of acetyl-CoA (belonging to SCFAs)↑	Alterations in MRS and GM function (synthesis of SCFAs) support the hypothesis that membrane dysfunction exists in schizophrenia	/	(52)

Summary of multimodal MR imaging studies investigating the relationship between the adult GM and brain function.

task designed to target a specific cognitive process. The so-called task-based fMRI paradigm tracks task-specific patterns of activition and yields important insights into how the brain responds to external stimulation. These stimuli can be visual, auditory, or other sensory modalities depending on the desired behavioral manipulation.

It is also well-known that the human brain is operational under resting conditions or in a relaxed state. Resting-state fMRI uses the BOLD signal to measure spontaneous fluctuations in the brain in the absence of conscious mentation (i.e., the "resting state") to reflect baseline neural activity in selected regions. This technique can also be used to construct global or local brain networks based on the identified interactions. Furthermore, analyses of functional connectivity (FC) between multiple spatially distributed brain regions have revealed different resting-state networks (functionally linked brain regions) that have specific functions and varied spatial topology. Despite the fact that different resting-state network studies have used various statistical methods (e.g., seeds, independent component analysis [ICA], or clustering), different groups of subjects, and/or diverse MR acquisition protocols (e.g., multiple vendors, multiple field strengths of 1.5T, 3.0T, or 4.0T), they have produced consistent results; this is indicative of the robust formation of functionally linked resting-state networks in the brain (40). One particular network that has received increasing attention is the so-called default mode network (DMN), which consists of functional links among the posterior cingulate cortex/precuneus, medial frontal regions, and inferior parietal regions. In contrast to the other resting-state networks, the DMN exhibits a high level of activity during rest and deactivates during the performance of cognitive tasks (41).

Functional neuroimaging has also been used to assess individuals with functional gastrointestinal disorders during gut stimulation. For example, peripheral factors such as gastrointestinal tract sensation, motility, and GM composition-associated mechanical and chemical signals (e.g., immune-related or endocrine signals) induce different functional changes in the brain that are related to the sensory processing of gut homeostatic conditions (e.g., in the brainstem sensory nuclei, thalamus, and posterior insula), emotional responses (e.g., in the locus coeruleus, amygdala, hippocampus, subgenual, and pregenual anterior cingulate cortices), and top-down modulation systems (e.g., in the periaqueductal gray [PAG], rostroventral medulla, prefrontal executive control area, and anterior midcingulate cortex) (42).

Magnetic Resonance Spectroscopy

In human patients with brain disorders, metabolic changes often precede anatomical changes. However, magnetic resonance spectroscopy (MRS) can provide unique information about the metabolic and neurobiological substrates of the brain, including the levels of N-acetylaspartate (NAA), choline (Cho), creatine (Cr), myoinositol (mi), glutamate (Glu) + glutamine (Gln), glucose, and GABA (43). In the adult brain, NAA is found almost exclusively in neurons and serves as a marker of neuronal density and viability, and changes in Cho resonance are commonly associated with diseases that alter membrane turnover and processes that are accompanied by hypercellularity. MRS has been applied to investigate a variety of neurological and neurosurgical disorders, including neoplasms, metabolic encephalopathy (hepatic encephalopathy [HE]), mitochondrial encephalopathy, and central neurodegenerative diseases (e.g., AD and PD) as well as psychiatric disorders, such as depression (44). Interestingly, using MRS on a 7T animal MRI system, Janik et al. (45) demonstrated that oral *Lactobacillus rhamnosus* increases the levels of central Glx, total NAA (tNAA; NAA + N-acetyl-aspartyl-glutamic acid [NAAG]), and GABA over different administration time courses. Additionally, proton MRS results in patients with Crohn's disease (CD) revealed higher Glu/total Cr (tCr; Cr + phosphocreatine) levels but lower GABA+/tCr levels in CD patients with abdominal pain compared to non-pain CD patients and healthy controls (46); these findings indicate that an imbalance between Glu and GABA may play a key role in abdominal pain processing. Taken together, these studies suggest that MRS is an appropriate and non-invasive technique that can be used to track neurochemical changes consequent to alterations of the gut microbiome.

Brain Iron Deposition Imaging

Iron is the most abundant metal in the brain and is actively involved in many fundamental biological processes, including oxygen transportation, DNA synthesis, mitochondrial respiration, myelin synthesis, and neurotransmitter synthesis and metabolism (47). Additionally, iron-mediated oxidative stress has been linked to motor system degeneration and cognitive impairments and is considered to be an important pathogenetic component of neurodegenerative diseases such as PD, AD, amyotrophic lateral sclerosis (ALS), and Huntington's disease (48, 53).

Due to the paramagnetic nature of iron, advancements in MRI techniques have opened a new window into *in vivo* iron deposition imaging of the human brain. Different MRI techniques and methods have been proposed for the visual and quantitative mapping of brain iron; these options include the visual rating of T2-weighted images, R2/R2* relaxometry (R2 = 1/T2 and R* = 1/R2), MR phase imaging, susceptibility-weighted imaging (SWI), and quantitative susceptibility mapping (QSM). Of these methods, R2* relaxometry and QSM have a high sensitivity for iron and a linear relationship with iron deposition (54, 55); however, only R2* relaxometry can distinguish calcifications from iron deposits.

It has been shown that commensal bacteria such as *Bifidobacterium longum* and *Bacteroides fragilis,* which are representative members of the GM, affect hepcidin expression, which is a central regulator of systemic iron metabolism. For example, using the SWI technique, Dong Lin demonstrated that patients with hepatitis B virus (HBV)-related cirrhosis, usually in a state of gut dysbiosis (17), exhibit decreased serum levels of hepcidin and an overload of systemic iron that are linked to the excessive accumulation of iron in the basal ganglia (56). However, there is a need for more detailed studies to fully explore the interactions between the GM, systemic iron metabolism, and brain iron deposition as well as the resulting effects in healthy human subjects.

Recently, De Santis et al. (22) proposed the novel term "radiomicrobiomics" for the combined analysis of large amounts of data (i.e., "omics") that represent an entire set of image-based brain signatures and features of microbiota. The data in this framework could be used to generate or test hypotheses and/or develop decision support tools associated with disease biomarkers and treatment. In addition to pre-clinical studies, emerging translational studies have also investigated crosstalk between the GM and CNS in humans. Future studies should incorporate measurements or interventions of gastrointestinal microbiota with neuroimaging modalities to elucidate this relationship further.

In the abovementioned studies, the enrolled subjects were from mainly healthy populations and the patient groups did not have significant gut disorders or had gut states that were similar to the control group (e.g., IBS patients). Additionally, of these studies, five were intervention studies; four required subjects to use probiotics for 4–6 weeks (25, 29, 50, 51), and one employed diet counseling (49). The assessments of brain function were mainly in the domains of cognition and mood, and included memory, executive function, attention, speed, depression, and anxiety tests. Although various neuroimaging strategies were used, most of these studies employed multimodal MRI approaches that involved both functional and structural MRI techniques. More specifically, the fMRI methods included resting-state fMRI or emotion- or cognition-induced task-based fMRI analyses of intrinsic brain activities and FC among brain networks whereas the structural MRI methods included DTI for white matter, R2* for iron deposition, and volumetric analyses. MRS was used to assess regional brain metabolism in two studies (27, 52).

Accumulating experimental evidence has shown that manipulation of the gut microbiome could modulate emotion, cognition, and/or behavior by modifying neurotransmitter levels, neuroinflammation, and brain functions (57, 58). Additionally, the administration of probiotics has been explored as a potential treatment strategy for neurological and psychiatric disorders in both experimental and clinical studies (59–62). For example, Messaoudi et al. (63) found that the consumption of a probiotic supplement *(Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) results in anxiolytic-like activity in rats and beneficial psychological effects in healthy human volunteers. However, corresponding human data from direct brain imaging sources remain scarce. Three studies have investigated the effects of probiotic administration on behavior, brain function, and gut microbial composition, two were in healthy volunteers (50, 51) and one was in IBS patients (29). Although there were no major changes in the general microbial diversity or evenness in the fecal samples in these studies, the administration of probiotics had definite effects on brain activity and FC that were associated with emotion and memory processing. Notably, probiotic administration is associated with the reduced engagement of an extensive brain network in response to an emotion recognition task (25) and emotional stimuli (29). Taken together, these results may provide novel approaches for the prevention and treatment of psychiatric disorders, including anxiety and depression.

In terms of brain microstructure, DTI is widely used to evaluate the integrity of white matter. Using rat models, Ong et al. (37) identified global changes in white matter structural integrity due to different diet patterns, i.e., standard/control diet, high fat diet, high fiber diet, and high protein/low carbohydrate diet. On the other hand, a study of healthy volunteers did not reveal any significant regional differences in FA or mean diffusivity (MD) after a 4-week probiotic intervention (51). Interestingly, two studies from Spain investigated the interactions between the GM, brain iron deposition (R2*), and cognitive performance in obese and non-obese subjects and found that GM diversity is negatively linked to R2* in the hypothalamus, caudate nucleus, and hippocampus (26, 49). Moreover, these authors reported that the changes in GM composition are associated with brain iron deposition and cognitive function. For example, increases in bacteria belonging to the *Tenericutes* phylum parallel decreases in R2* gain in the striatum and better visuospatial constructional ability (49). These authors speculated that the bacterial metabolization of arsenic and the generation of siderophores were the mechanisms underlying these protective associations.

Regarding neurological disorders, hepatic encephalopathy (HE) presents as a spectrum of neuropsychiatric symptoms that range from subtle fluctuations in cognition to coma (64). Alterations in the GM as well as related metabolomes, such as amino acid metabolites and endotoxins, could lead to the occurrence of HE when occurring against a background of intestinal hyperpermeability (i.e., leaky gut) and systemic inflammation. Using a combination of cognitive testing, assessments of stool microbiota, brain MRI analyses, and evaluations of systemic inflammation, Ahluwalia et al. (28) identified a robust correlation network in which autochthonous bacterial families (*Lachospiraceae, Ruminococcaeae,* and *Clostridiales XIV*) are negatively correlated with liver function and glial MRS manifestations of ammonia (high Glx levels with low mi and Cho levels) in the brain, especially in subjects with HE. The same research group assessed elderly outpatients with or without cirrhosis and found that elderly patients had an altered gut-brain axis regardless of the presence of cirrhosis, which suggests that cognitive function is influenced by alterations in the GM *per se*. In another study, MRS was used to evaluate the metabolic and neurobiological substrates of the brain, and the amnestic/non-amnestic group had a decreased mi/Cr ratio and a reduced NAA-NAAG/Cr ratio in the anterior cingulate cortex. The cognitively impaired groups had a significantly lower relative abundance of genera belonging to autochthonous and beneficial taxa (27). Additionally, several studies have performed measurements of microbial or human metabolites, serum inflammatory markers, and plasma β-amyloid [1–42; (Aβ42)] to clarify the molecular mechanisms underlying these relationships. A 2-year longitudinal study by Blasco et al. (49) revealed that increases in circulating Aβ42 levels are positively associated with *Tenericutes* and *Thermodesulfobacteria* RA as well as improvements in visuospatial constructional ability and immediate memory but negatively correlated with increases in

R2*, which may have great significance for further understanding the pathogenesis of AD.

The studies included in the present review have several limitations. First, the numbers of subjects were relatively small in most of the studies included in this review. Further studies are needed in larger number of patients to define the real effect of these changes on outcomes. Second, the samples were non-invasively obtained via direct collections of stool, which allows for the detection of a wide range of intestinal microflora but cannot differentiate between the luminal and mucosal environments, less local microenvironments, or regional differences throughout the gut. Due to the difficulty and expense associated with obtaining local tissue specimen, studies characterizing the human mucosal-associated microbiota was limited. Samples from endoscopic mucosal biopsy can directly reflect mucosal environments, and it has been reported that the composition of luminal and mucosal-associated microbiota was different both in health and certain disease states (65, 66). In particular, Keshavarzian et al. showed the mucosal and fecal microbial community of Parkinson's disease patients was significantly different from control subjects, with the fecal samples showing more marked differences than the sigmoid mucosa (67). Thus, it is important to investigate and compare the microbiota of luminal and mucosal niche. Third, the possible influences of usual diet, drugs, and exercise were not assessed. However, most studies excluded those subjects who had the history of using probiotics, prebiotics, synbiotics, or antibiotics for at least 1 month before fecal sample collection. On the other hand, body mass index between study groups was compared in some studies (30, 49). Fourth, the phylogenetic

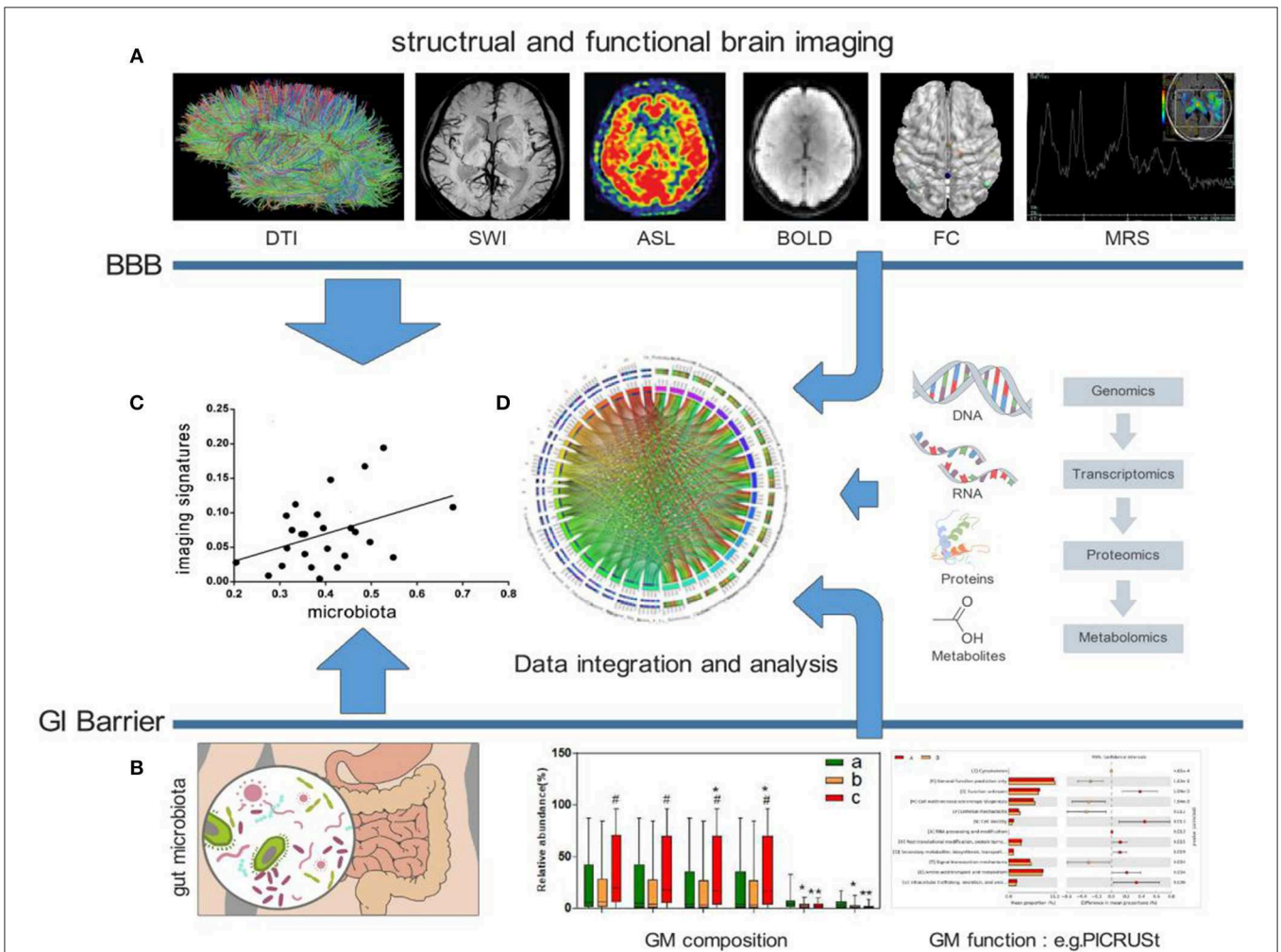

FIGURE 1 | Possible frameworks for exploring crosstalk between the GM and human brain. **(A)** Examples of distinct MRI maps: DTI, SWI, ASL, BOLD, FC, and MRS (from left to right). **(B)** Analysis of the GM, including composition and function. **(C)** Explorations of the direct association between the GM and human brain imaging. **(D)** Combining other "omics" techniques, such as metabolomics and proteomics, to generate a complete picture of host and microbial pathways. DTI, Diffusion Tensor Imaging; SWI, Susceptibility Weighted Imaging; ASL, Arterial Spin Labeling; BOLD, blood oxygenation level dependent; FC, functional connection; MRS, Magnetic Resonance Spectroscopy; BBB, blood-brain barrier; GI, gastro-intestinal; GM, gut microbiota; PICRUSt, Phylogenetic Investigation of Communities by Reconstruction of Unobserved States.

power of the 16S rRNA gene sequencing analysis was low at the species level, which requires careful treatment, and should be replicated by future metagenomics sequencing. Metagenomics is the most recent development in the study of the gut microbiota. It can provide higher taxonomical resolution than 16S rRNA sequencing, reaching the species and strain levels. Further more, it can also characterize the function of a given community (23, 68).

CONCLUSIONS AND FUTURE PERSPECTIVES

Taken together, the studies included in this review indicate that the human GM profile is significantly associated with brain microstructure, intrinsic neural activities, and brain FC as well as cognitive function and mood. Well-designed longitudinal studies that include assessments of the gut microbial community structure and microbial metabolomics in conjunction with neuroimaging and behavioral testing will be required to establish directionality and causality. Furthermore, additional measures of inflammation, immune activation, neurotransmitters, neuromodulators, microbial metabolomics, and intestinal permeability, motility and visceral sensitivity will be useful for elucidating the interactions between the gut and brain. Future studies should also aim to integrate multiple "omics" techniques (69), such as metabolomics and proteomics, to generate a complete picture of host and microbial pathways (**Figure 1**).

AUTHOR CONTRIBUTIONS

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frontiers in Neurology

BRIEF RESEARCH REPORT
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Processing of Emotions in Functional Movement Disorder: An Exploratory fMRI Study

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Background: Affective dysregulation and impaired cognitive control are implicated in the pathology of functional neurological disorders (FNDs). However, voluntary regulation of emotions has seldom been researched in this group of patients. We hypothesized that patients with FNDs use inefficient voluntary emotion regulation strategies and regulate emotional reactions via increased motor activation.

Methods: Fifteen patients with functional movement disorder (FMD) and fifteen healthy subjects matched by age, sex, and education underwent an emotion regulation task in fMRI. For stimuli, we used neutral and negative pictures from the International Affective Picture System. There was no restriction on their emotion regulation strategy. Both patients and healthy subjects were asked about the strategies they had used in a post-scanning interview. Participant levels of depression, trait anxiety, and alexithymia were assessed.

Results: There were no significant differences in the emotion regulation strategies used by patients and healthy subjects, nor in levels of reported alexithymia and depression. However, patients showed increased activation in several brain areas when observing negative pictures, notably in the post-central gyrus, precuneus, posterior cingulate cortex (PCC) and cerebellar vermis, and also in their emotion regulation condition, particularly in the precuneus and post-central gyrus. Alexithymia was negatively associated with left insular activation during the observation of unpleasant stimuli only in the patient group.

Conclusions: Our findings may implicate areas associated with self-referential processing in voluntary emotional regulation and lower emotional awareness as having a role in patients with functional movement disorders. However, our findings must be replicated with larger sample.

Keywords: emotion regulation, functional neurological disorder, neuroimaging, alexithymia, precuneus

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INTRODUCTION

A functional neurological disorder (FND) is a condition in which a patient has neurological symptoms in the absence of neurological disease. FND spans a variety of symptoms such as non-epileptic seizures, abnormal movements (gait disorders, tremor, dystonia, etc.), weakness, and sensory symptoms. Even after more than 100 years of research interest, a pathological mechanism underlying FND is still a subject of debate.

A growing body of neuroimaging evidence supports the notion that abnormal emotional processing is a key factor in the etiology of functional neurological symptoms (1, 2). Task-based neuroimaging studies show limbic and paralimbic hyperactivation (3–5), abnormal limbic-motor circuit connectivity (4–6), and altered activation of several prefrontal regions in emotion processing tasks in various groups of patients with FND (3, 6–9). These findings suggest that unregulated emotional reactions may exert an abnormal influence on the motor system.

Following Janet (10) and Ludwig (11), contemporary cognitive models afford a central role in attentional processes in the etiology of FND (12, 13). There is evidence that both higher-level endogenous attention control and lower-level automatic attentional orienting are impaired in FND. Deficits in voluntary attentional disengagement from emotionally neutral stimuli (14) and the abnormal automatic (pre-conscious) allocation of attention to facial affect (15), specifically to threat-related facial affect (16), were found in FND patients. Moreover, avoidance learning of negative stimulus was shown to be impaired in FND (17). These findings demonstrate that FND patients show diminished cognitive processing in emotional contexts.

Taken together, the emerging model that could help in understanding FND combines higher-order (attention, cognitive control) and bottom-up limbic processes (limbic hyperactivity, limbic-motor connectivity) interacting to influence motor control (18). Despite research evidence of impaired cognitive processing in emotional contexts, only minor research focus has been given to voluntary emotional regulation in FND. Voluntary emotional regulation refers to intentional up or down-regulation of an emotional reaction and it is contrasted to automatic (non-conscious) voluntary regulation such as an avoidance of stimulus (19). To our knowledge, only one neuroimaging study utilizing magnetoencephalography examined voluntary emotional regulation in FND, with a finding of reduced fronto-cortical, but enhanced sensorimotor involvement in emotion regulation efforts (20). This finding suggests that the patients had lower cognitive control over emotional stimuli and may activate different ("less cognitive") emotion regulation strategies, reflected in sensorimotor network activation even though the authors of the study restricted the task to cognitive reappraisal of emotional stimuli. Opitz et al. (21) point to the fact that people in laboratory settings are likely to use whichever emotion-regulation strategies work best for them even when they have been trained and instructed to use one specific strategy.

Given the abnormal attention to emotional stimuli reported in FND, patients may use attentional deployment (e.g., avoidance) or emotional reaction suppression as ways to regulate emotional reactions. For example, Ferri et al. (22) found that diverting attention from unpleasant emotional stimuli also predominantly activates the parietal regions in healthy subjects, similarly to findings in FND reported by Fiess et al. (20). Suppression of emotion-expressive behaviors was shown to reduce negative emotional experiences but sustain elevated responses in the amygdala (23); this finding is also relevant to FND, as failure to habituate the amygdala in response to emotional stimuli was observed in this group of patients (5). We hypothesize that the hyperarousal and diminished habituation of the amygdala documented in FND may be associated with inefficient voluntary emotional regulation. We therefore conducted an exploratory study aimed at identifying the natural emotion regulation strategies ["spontaneous regulation"; (24)] employed by FND patients and to explore brain activation related to the voluntary emotion regulation in this group of patients.

MATERIALS AND METHODS

Participants

For the purpose of the study, we selected a sub-population of FND with predominant motor signs to ensure relative sample homogeneity. Fifteen adult patients with clinically definite functional movement disorder (FMD), diagnosed based on established clinical criteria (25), were recruited from the neurology clinic at Masaryk University together with fifteen healthy controls recruited from the general population and matched with the patients by sex, age, and education. The sample size was determined on the basis of previous neuroimaging research utilizing emotional stimulation in FMD patients (e.g., (5), $N = 16$; (6), $N = 12$; (7), $N = 10$; (8), $N = 12$) and also on the basis of the emotion-regulation study that reported sample sizes of 18 per group as sufficient to gain statistical power of 80% (26). Only patients with symptoms persisting for more than 2 years and healthy volunteers with no previous neurological or psychiatric symptoms were included in the present study. Demographic and neurological data were recorded, and depression, trait anxiety, and alexithymia, defined as restricted access to emotional information (27), were evaluated. Patient clinical characteristics are summarized in **Table 1**. All participants gave their written informed consent and received monetary compensation. The study was approved by the ethics committee of Masaryk University and St. Anne's Hospital.

Self-Report Measures

Beck Depression Inventory

Since depression is a common comorbidity in FND (28), we included the Beck Depression Inventory, second version [BDI-2; (29)] to control for the influence of reported depression on emotional regulation. BDI-2 is a widely used 21-question multiple-choice self-report inventory with high internal consistency (30) that measures characteristic attitudes and symptoms of depression.

State-Trait Anxiety Inventory

The trait scale from the State-Trait Anxiety Inventory [STAI-T; (31)] was used to measure the trait of anxiety. The scale consists

TABLE 1 | Clinical and demographic characteristics of functional movement disorder patients.

Patient	Clinical signs	Gender	Age	Illness duration	Comorbid affective disorder	Medication
1	Dystonia	F	52	4	Depressive syndrome, panic attacks	Venlafaxine
2	Body stiffness and spasms	F	46	4	Depressive syndrome	Oxazepam and SSRI
3	Tremor of right hand	F	56	11	None	None
4	Right leg weakness	M	20	3	None	None
5	Quadriparesis	F	59	2	None	None
6	Gait disorder	F	63	5	None	None
7	Myoclonus	F	61	15	None	None
8	Tremor of right hand	F	51	2	None	None
9	Tremor of both hands, gait disorder	F	31	2	Depressive syndrome	None
10	Tremor, abnormal movements of chin	F	22	3	None	None
11	Myoclonus	M	20	2	None	None
12	Gait disorder	F	29	6	None	Agomelatine
13	Weakness of both legs, non-epileptic seizures	M	41	8	Depressive syndrome, anxiety	Mirtazapine
14	Tremor and dystonia	M	24	2	None	None
15	Weakness of both arms, non-epileptic seizures	F	21	4	None	None

Comorbid affective disorder refers to presence of clinically significant symptoms of anxiety or depression assessed by a clinical psychologist. F, female; M, male. Age and illness duration is displayed in years.

of 20 statements that are rated on a four-point Likert scale. STAI-T scores were used as a covariate to control for the effects of anxiety, which is commonly associated with the tendency to experience somatic symptoms (32).

Toronto Alexithymia Scale

Alexithymia has been shown to limit emotional regulation in healthy subjects as well as in patient samples (33, 34). FMD patients have been found to be significantly more alexithymic than patients with organic motor disorders and healthy controls (35), so we included a measure of alexithymia in the study as a factor potentially contributing to emotional dysregulation in FMD. The Toronto Alexithymia Scale [TAS-20; (36)] is a well-validated and commonly used measure of alexithymia. TAS-20 is a multidimensional self-report instrument with a three-factor structure: difficulty identifying feelings, difficulty describing feelings, and externally oriented thinking. Items are rated using a 5-point Likert scale and the total score of alexithymia is calculated as a sum of the three subscales.

Emotion-Regulation Task

Stimuli

Emotional and neutral pictures from the International Affective Picture System [IAPS; (37)] and emotionally negative pictures were selected with an emphasis on scenes with threat-related content (e.g., frightened people, weapons, attacks, surgical procedures), as threat sensitivity was repeatedly observed in patients with functional neurological symptoms (7, 16, 38). The selected negative pictures had mean normative valence ratings of 2.54, and mean arousal ratings of 5.66. Selected neutral images had mean valence ratings of 5.10 and mean arousal ratings of 3.26 (see **Supplementary Material**).

Task Design

At the start of each trial, a picture was presented with an instruction word displayed below the picture ("look"; 3 s); the instruction remained for the next 5 s for neutral pictures and negative pictures without regulation, or the instruction changed to the regulation instruction ("decrease," 5 s) for negative pictures with regulation. The presentation of each picture was followed by 1 s of blank screen, followed by a self-reported rating of the strength of the negative effect (on a scale from 1 to 4, where 1 was labeled "not at all" and 4 was labeled "very much"; 3 s), finally the word "relax" appeared on a blank screen for the rest of the trial (9 s). The task design follows a methodology used by Jackson et al. (39) and is depicted in **Figure 1**. Responses were made on a 4-button box using the participant's dominant (right) hand. The combinations of instructions and pictures produced three trial types: decrease negative (regulation), look negative (non-regulation), and look neutral (non-emotional). A total of 66 trials (22 of each trial type) were administered in pseudo-randomized order with the constraint that no more than two of any trial type or picture type followed each other sequentially. The task was presented with E-Prime (Psychology Software Tools Inc, Pittsburgh).

Procedure

Pre-MRI, participants completed questionnaires and were familiarized with the task by practicing several rounds of the task with a different set of IAPS pictures than those used with the MRI. The participants were not given any specific instructions for emotion regulation strategies to use but were only asked to try to down-regulate an emotion that might occur in the reaction to the presented pictures. The participants were also informed about a post-scanning interview about the emotion regulation strategies they applied during the task. In the post-scanning interview, the responses of participants were coded into three categories

FIGURE 1 | Scheme of the task design. Neutral and negative pictures were first presented with a "look" instruction for 3 s. In neutral pictures and half of the negative pictures the "look" instruction remained on the screen for another 5 s. In the other half of negative pictures, the instruction "look" changed into "regulate" instruction after initial 3 s of picture viewing.

based on a process model of emotional regulation (40). The categories were: attentional deployment, cognitive reappraisal, and emotional response modulation. Attentional deployment refers to focusing on non-emotional details of a picture or focusing on one's own thoughts unrelated to a picture. Cognitive reappraisal involves reinterpreting the meaning of the emotional stimulus (e.g., a gun on a picture is reinterpreted as a mock-up weapon). Emotional response modulation refers to efforts to modify an emotion after it has been fully generated; volitional inhibition of verbal and behavioral expressions of emotions is the most frequent form of this strategy.

MRI Data Acquisition

MRI scanning was performed using a 3-Tesla whole-body MRI scanner SIEMENS MAGNETOM Prisma (Siemens Medical Systems, Erlangen, Germany) at the Central European Institute of Technology, Brno, Czech Republic. At the beginning, a high-resolution anatomical T1-weighted scan was acquired with the following parameters: magnetization-prepared rapid gradient-echo (MPRAGE) sequence [repetition time (TR) = 2,300 ms, echo time (TE) = 2.33 ms, flip angle (FA) = 8°, voxel size 1.00 × 1.00 × 1.00 mm, slice thickness 1.00 mm, matrix 240 × 224 × 224]. Subsequently, whole brain functional measurement was performed by multiband acquisition with the parameters: TR = 642 ms, TE = 35.0 ms, FA = 47°, voxel size 3.3 × 3.3 × 3.5 mm, 40 sagittal slices, field of view 210 × 210 mm. The total number of volumes was 2,175.

Analysis of Self-Report and Behavioral Data

A statistical analysis was performed using Python numerical and statistical libraries. The variables were first tested for normality using the Shapiro-Wilk test. The variables that were not normally distributed were log-transformed. For continuous data, a two-way analysis of variance (ANOVA) was used to test for differences across the two groups and three task conditions with *post-hoc* Bonferroni pairwise comparisons when significant. The χ^2-test was used for categorical data and the Pearson correlation coefficient (r) was used to examine potential associations between behavioral and neuroimaging findings. Bonferroni correction was applied to correct for multiple comparisons.

Analysis of fMRI Data

MRI data were processed and analyzed using SPM12 (Welcome Department of Cognitive Neurology, London, UK). The preprocessing of fMRI images included realignment to correct for head movements. Subsequently, co-registration of functional and anatomical images and interpolation in time were performed, followed by the spatial normalization into the stereotactic Montreal Neurological Institute (MNI) space and spatial smoothing (isotropic Gaussian kernel of 8 mm full-width at half-maximum). The motion related artifacts were regressed from the data by setting up a general linear model design using 24 motion parameters (41).

In the first level of analysis, six separate regressors in the generalized linear model were specified for fMRI responses to the initial negative or neutral stimulus viewing; further attending to neutral or negative stimulus; regulation of negative stimulus; and blank screen. Individual statistical parametric maps were calculated for the following contrasts of interest in order to investigate BOLD signal changes: negative-look vs. neutral-look contrast for the effect of emotional stimuli (initial negative or neutral stimulus) and negative-regulate vs. negative-look contrast for the effect of emotion regulation (regulation of negative stimulus or further attending to negative stimulus). Values for both contrasts were subjected to second-level analysis.

To obtain the second level between-group z-statistics, statistical maps were thresholded at a z value > 3.2 (cluster forming threshold, $p < 0.001$) and a cluster-corrected FWE correction threshold ($p < 0.05$) was calculated using Gaussian random field theory. We performed an ANCOVA to test for differences in the two contrasts. Age, sex, BDI, and STAI were used as nuisance variables. Due to the exploratory nature of the study, we report both significant clusters ($p < 0.05$) after FWE correction and uncorrected results with $p < 0.001$ threshold the cluster level.

RESULTS

Participant Characteristics and Behavioral Findings

In total, the study had fifteen patients (eleven females) with a mean age of 39.7 (SD = 16.5) years. Demographic and clinical characteristics are provided in **Table 1**. Fifteen HCs (eleven

TABLE 2 | Descriptive statistics for the self-report and behavioral variables.

Variable	FMD	HC	Statistics
Mean age (SD)	39.73 y (16.54)	40.27 y (15.88)	$t_{(28)} = 0.09$, $p = 0.93$
Mean symptom duration	4.87 y (3.80)		
BDI-2	22.93 (12.92)	16.29 (8.40)	$t_{(28)} = 1.61$, $p = 0.12$
STAI-T	40.80 (12.24)	32.86 (7.48)	$t_{(28)} = 2.12$, $p = 0.04$
TAS-20	46.33 (12.55)	41.71 (12.42)	$t_{(28)} = 0.10$, $p = 0.33$
Neutral-look	36.40 (13.10)	33.13 (11.63)	
Negative-look	38.67 (13.60)	43.60 (11.61)	
Negative-regulation	39.13 (13.94)	43.47 (13.72)	
Attentional deployment	11 (36.7%)	9 (30%)	
Cognitive reappraisal	4 (13.3%)	5 (16.7%)	
Reaction modulation	0 (0%)	1 (3.3%)	

BDI-2, Beck depression inventory; STAI-T, trait scale from the State-Trait Anxiety Inventory; TAS-20, Toronto alexithymia scale.

females) had a mean age of 40.3 (SD = 15.9) years. Patients and HCs did not differ significantly with respect to age, gender, or education. As expected, more patients used psychotropic medication. Patients had higher scores than HCs on both the STAI-T and BDI-2 scales. There was no significant difference in TAS-20 between patients and HCs, suggesting low alexithymia in our sample (see **Table 2** for further details).

To test possible group and task condition differences in negative emotion rating induced by stimuli (IAPS pictures), we conducted a two-way ANOVA with group (patients, HCs) and task condition (neutral-look, negative-look, negative-regulate) as between-subject factors. There was no interaction effect [$F_{(2,84)} = 0.93$, $p = 0.398$], nor mean effect of group [$F_{(1,84)} = 0.670$, $p = 0.414$], but ANOVA revealed a significant main effect of the task condition on negative emotion rating [$F_{(2,84)} = 3.62$, $p = 0.031$]. *Post-hoc* comparisons using Tukey's HSD test indicated that the mean score for the rating in the negative-look condition (M = 41.13, SD = 12.68) was significantly different than the rating in the neutral-look condition (M = 34.8, SD = 12.29). However, there was no significant difference between neutral-look and negative-regulate, nor between negative-look and negative-regulate conditions. These results indicate that the induction of negative emotional experience was successful in both groups, but the down-regulation of emotion was unsuccessful. Moreover, the compared groups (FMD vs. HC) do not differ in the task conditions.

We also compared the frequency of emotion regulation strategies reported by patients and HCs in the post-scanning interview. The strategies were clustered into three categories: attentional deployment, cognitive reappraisal, and emotion-response modulation. The strategies used were not significantly different between HCs and patients [$\chi^2_{(2)} = 1.311$, $p = 0.519$]; both groups used attentional deployment as most preferred emotional regulation strategy (see **Table 2**).

Imaging Findings

No data were discarded due to motion-related or other artifacts. With the negative-look vs. neutral-look contrast (effect of emotion induction), regional differences were found between the FMD vs. HC group when controlling for depression and anxiety but only at a lower statistical threshold (uncorrected $p < 0.001$). Notably, the FMDs showed increased activation in left postcentral gyrus, right superior parietal lobe/precuneus, left PCC, and right cerebellar cortex. We also observed decreased activation in the bilateral insula in FMD patients as compared to HCs. There were no significant activations in the reversed comparison.

In the negative-regulate vs. negative-look contrast, no differences between the FMD and HC group survived FWE correction; however, FMD patients showed increased activation in two regions at a lower statistical threshold ($p < 0.001$ uncorrected). The effect of emotional regulation specific to FMD patients was underpinned by increased activity in the right superior parietal lobe/precuneus and left postcentral gyrus (see **Table 3**).

Despite the moderate levels of alexithymia in both FMD and HC groups, we tested for potential differences in association between scores in TAS-20 and activations in FMD and HCs in both reported contrasts, as alexithymia has been shown to influence emotional regulation. Although the TAS-20 scores did not vary between groups (**Table 2**), alexithymia was found to differentially influence activation in the left insula in the FMD and HC groups. FMD patients exhibited decreased activation in the left insula in negative-look vs. neutral-look contrast with increasing levels of alexithymia (**Figure 2**); $r = -0.74$, $p = 0.0018$ (with $p < 0.003$ threshold after Bonferroni correction for multiple tests). The correlation between alexithymia and left insula activation was not significant in HCs; $r = 0.016$, $p = 0.96$. No other significant associations were found between TAS-20 scores and task-related brain activations.

DISCUSSION

The current study examined neural activation associated with uninstructed voluntary emotional regulation in FMD patients. We also examined the association between alexithymia and the ability to regulate emotions in FMDs. We successfully induced emotional response in the participants, but emotion regulation did not decrease negative feelings across the groups. There were no differences in negative emotional experience induced by stimuli between FMDs and HCs. We observed several differences in brain activations between FMDs and HCs but only on a more liberal statistical threshold. In comparison to HCs, FMD patients showed increased activation in the right superior parietal lobe/precuneus and in the left post-central gyrus during emotion regulation attempts (relative to observing negative stimuli). Increased activation in the right superior parietal lobe/precuneus and in the left post-central gyrus was observed in FMD also during observation of negative stimuli compared to neutral pictures.

Bilateral superior parietal lobe/precuneus activation has been documented during focusing on both arousing and non-arousing regions of unpleasant images in healthy subjects and is therefore implicated in the emotion regulation strategy of attentional

TABLE 3 | fMRI results for the negative-look (NegL) > neutral-look (NeuL) and negative-regulate (NegR) > negative-look (NegL) contrasts for the functional movement disorder (FMD) > healthy control (HC) comparison.

Comparison	Contrast	Cluster mm^3	t^+	MNI			Side	Region	Talairach
				x	y	z			
FMD>HC*	NegL>NeuL	72	4.72	−22	−32	76	L	Post-central gyrus	
		192	4.15	28	−42	64	R	Precuneus	BA 7
		152	4.12	−12	−34	44	L	Post-cingulate gyrus	BA 31
		176	4.06	−40	−8	20	L	Insula	
		144	4.04	42	−14	−8	R	Insula	
		48	3.76	20	−58	−50	R	Cerebellar lobule VI	
FMD>HC*	NegR>NegL	304	4.35	16	−70	64	R	Precuneus	BA 7
		16	3.85	−22	−32	76	L	Post-central gyrus	

There was no significant activation in the opposite direction.
$p < 0.001$ uncorrected.
+The t value indicates the peak statistical value for the cluster.
MNI, Montreal Neurological Institute.

deployment (22). Both FMD patients and HCs in our study used attentional deployment as the most preferred emotion regulation strategy with no significant differences between groups. However, only the FMD group showed increases in precuneus activation that was also present during exposure to negative stimuli without regulation instruction. The precuneus is considered to be a part of the default mode network and has been associated with self-monitoring and consciousness (42). Activity in medial parts of the precuneus has been elicited in tasks involving motor imagery (43, 44) and episodic memory retrieval (45, 46). In FND, activation in the precuneus was reported during attempts to move in functional paralysis with selective changes in functional connectivity of the motor cortex with the precuneus during functional paralysis (47). We therefore suggest that the observed activations in the right precuneus together with the left postcentral gyrus may reflect implicit emotional processing rather than voluntary attention control (e.g., focusing on non-arousing aspects of pictures). Neither option can be ruled out; this should be a subject of future research. Moreover, the precuneus has been implicated in dissociative phenomena associated with abnormal self-awareness. Nicholson et al. (48) found increased resting-state precuneus-amygdala activation in the dissociative subtype of posttraumatic stress disorder and increased precuneus activation was also reported in hypnotically induced limb paralysis (47). Our findings may further corroborate dissociation theories highlighting a role of self-monitoring and self-related mental representations during voluntary efforts in FND.

Several brain areas were differentially activated in FMDs and HCs while observing unpleasant pictures as compared to neutral pictures. In addition to increased activation in the right precuneus and left post-central gyrus, we also observed increased activation in the left PCC and right cerebellar lobule VI in FMD patients as compared to HCs. Increased PCC activation was observed in FND in the emotional induction paradigm (7), during motor preparation in functional paralysis (47) and also in functional tremor (49). Moreover, the PCC was implicated in self-reflection (50) and in the integration of emotion and memory (51). Specifically in FND, Blakemore et al. (7) interpreted increased PCC activation as an abnormal access to self-relevant information in memory which can further modulate action readiness. Furthermore, we observed increased cerebellar activation in right lobule VI in the FMD patients. Lobule VI has been associated with processing aversive stimuli in the form of activating motor plans associated with action preparedness (52). Taken together, observed increased PCC and cerebellar activation may thus be indicative of instinctive behavioral responses to threat-related information in FND, as was formulated by Kretschmer (53).

Interestingly, we found decreased insular activity during exposure to negative stimuli in FMD patients as compared to HCs. Although there were no differences in levels of alexithymia between FMDs and HCs, we found that the activation in the left insula was negatively correlated with levels of alexithymia only in the FMD group. Functional neuroimaging studies employing emotionally arousing stimuli such as disgusting, frightening, or sexual pictures have consistently reported activation in the insula in healthy subjects (54). Furthermore, alexithymia is commonly seen in patients with functional deficits of the insular cortex such as frontotemporal dementia (55) and autism (56), and under activation of the insula has been associated with deficits in emotional awareness (57). Taken together, our findings may point to low emotional awareness in FMD patients and their tendency to react to unpleasant stimuli more physically, as reflected in the increased cerebellar and PCC activation in FMD patients during exposure to negative stimuli.

Contrary to previous research (3–5), we did not observe amygdala hyperactivation in FMDs in emotion induction contrast. However, recent research studies utilizing IAPS stimuli also failed to find differential response in amygdala between healthy subjects and FMD (7), functional dystonia (8) and functional tremor patients (9). Similar to our findings, Espay et al. (8) reported decreased right insular activation in response to emotional stimuli together with decrease

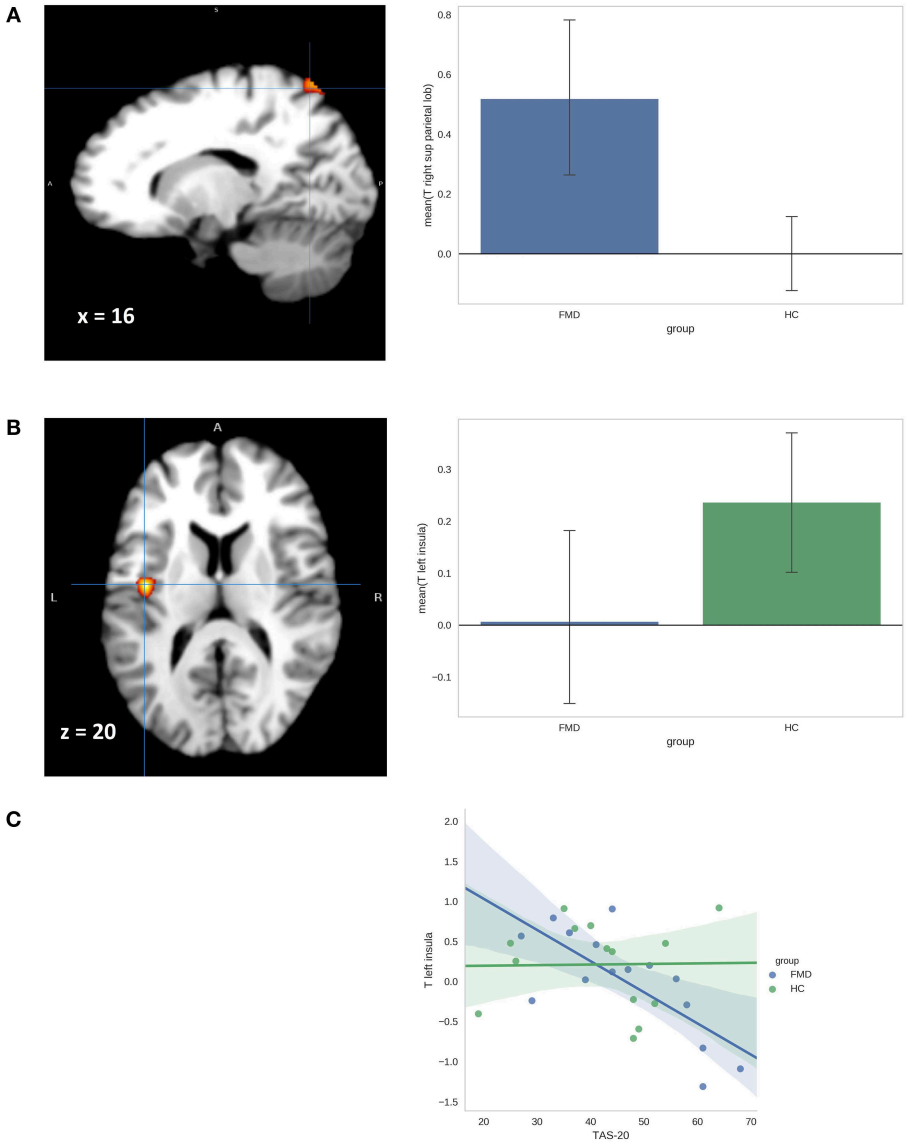

FIGURE 2 | (A) Activation map and adjacent barplot demonstrate group differences in activation of the left superior parietal lobus in the negative-regulate>negative look contrast. **(B)** Activation map and adjacent bar-plot shows group differences in the left insula activation in the contrast negative-look>neutral-look. **(C)** Scatterplot shows the relationship between *t*-values for the negative-look>neutral-look contrast in left insula and TAS-20 scores for FMD patients and HCs.

in activation in bilateral precuneus in functional dystonia compared to healthy subjects. Research studies reporting amygdala hyperactivation in FND used facial expressions as stimuli to induce the activation (3–5). The amygdala routinely responds to novel stimuli (58, 59) and Somerville and Whalen (60) noted that amygdalar response to facial stimuli such as Ekman faces (61) may represent reaction to novelty as these facial expressions are not genuine and therefore not typically seen in daily life. Hyperactivity of amygdala observed in FND patients may thus represent abnormal reaction to novel stimuli but may not be related to environmentally meaningful emotional responses such as defense reactions.

Several limitations of the present study have to be addressed. First, the presented results need to be interpreted cautiously due to relatively small sample size. However, small sample sizes are common in neuroimaging research of FND due to difficulties in patient recruitment and aberrant movements often precluding MRI measurement. Due to the limited sample size we could not cluster patients and healthy controls according to the emotion regulation strategy they used, and we were unable to determine the effects of emotion regulation strategy on the patterns of brain activation. Future studies could focus on comparing different emotion regulation strategies within a group of FND patients (such as emotional suppression or avoidance of emotional stimuli). The depression scores in our

control group were relatively high, with average scores in the range of mild depression. This result might indicate a presence of emotional dysregulation in HCs; however, over-reporting of depression in BDI-2 is also possible. The influence of depression on the results is not probable as there is a non-significant difference in BDI-2 between HCs and FMDs, and we also controlled for the effect of depression in the neuroimaging analysis. We did not assess a level of trauma in the participants of our study. The nature of chosen emotion stimuli (e.g., violent scenes) may evoked past traumatic experiences especially in the FMD group, where trauma rates are found to be higher than in the general population (62). Evoked traumatic experiences may consequently influence emotion-regulation (63) and reporting in the post-scanning interview. Even though we were careful to make sure the participants understood the task, a realization of how one regulates emotion is inherently a difficult task without a previous intensive training. Moreover, given a low emotional awareness observed in FND (35, 64), a reliability of self-reported emotional experience (depression, alexithymia, negative feeling reports) is problematic in this group of patients (24). Taken together, failure to detect differences in self-reports between FMDs and HCs may be caused by small sample size but also by patients' difficulties providing reliable reports of their emotional experience and regulation process. Finally, we included patients with a broad range of functional movement symptoms which may preclude isolating a pathophysiological mechanism underlying specific symptom presentation (8, 9). However, Edwards (65) pointed out that functional neurological symptoms commonly co-occur and a unifying pathophysiology is therefore likely across different functional symptom phenotypes. For this reason, the division of FND based on prevalent motor symptoms may be seen as rather artificial. Our results, if replicated, point to a more general mechanism underlying abnormal emotional processing in FND patients.

CONCLUSION

Our study suggests an abnormal involvement of areas implicated in self-referential processing during voluntary emotional regulation efforts and limited access to emotional experience in FMD patients. Our results may indicate that emotional reactions to negative stimuli are inaccessible for conscious processing due to low emotional awareness and the implicit emotional reactions may therefore pose a difficulty for voluntary emotional regulation efforts. As a result, more bodily emotional regulation processes such as aberrant movements ma develop instead in FMD patients in order to decrease accumulated arousal. A similar view was postulated by Janet (10): "Action, by becoming unconscious in hysterics, by separating from consciousness...assumes an appearance that recalls the action of visceral muscles..." (s. 137). However, the findings presented in this study have to be considered preliminary due to the small sample size and the liberal statistical threshold used in neuroimaging analyses. Future studies should employ experimental tasks probing emotional awareness to further elucidate the role of (un)conscious emotional processing in affective dysregulation in FNDs.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of the University Hospital of St. Anne and Institutional Review Board of the Masaryk University, Brno, Czech Republic.

AUTHOR CONTRIBUTIONS

The first draft of the paper was written by PS. ML designed the emotion regulation task and JL performed MRI analyses. MBar, TK, MBrá, MBal, and MS critically revised and commented on the manuscript and figures. JK and JF recruited patients and healthy controls. All the authors substantially contributed to and have approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00861/full#supplementary-material

Table S1 | Pictures from IAPS selected for the task.

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A Functional Neuroimaging Meta-Analysis of Self-Related Processing in Schizophrenia

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Background: Schizophrenia is characterized by self-disturbances, including impaired self-evaluation abilities and source monitoring. The cortical midline structures (e.g., medial prefrontal cortex, anterior and posterior cingulate cortex, and precuneus) and the temporoparietal junction are known to play a key role in self-related processing. In theory, self-disturbances in schizophrenia may arise from impaired activity in these regions. We performed a functional neuroimaging meta-analysis to verify this hypothesis.

Methods: A literature search was performed with PubMed and Google Scholar to identify functional neuroimaging studies examining the neural correlates of self-processing in schizophrenia, using self-other or source monitoring paradigms. Fourteen studies were retrieved, involving 245 patients and 201 controls. Using peak coordinates to recreate an effect-size map of contrast results, a standard random-effects variance weighted meta-analysis for each voxel was performed with the *Seed-based d Mapping* software.

Results: During self-processing, decreased activations were observed in schizophrenia patients relative to controls in the bilateral thalamus and the left dorsal anterior cingulate cortex (dACC) and dorso-medial prefrontal cortex. Importantly, results were homogeneous across studies, and no publication bias was observed. Sensitivity analyses revealed that results were replicable in 93–100% of studies.

Conclusion: The current results partially support the hypothesized impaired activity of cortical midline brain regions in schizophrenia during self-processing. Decreased activations were observed in the dACC and dorsomedial prefrontal cortex, which are involved in cognitive control and/or salience attribution, as well as decision-making, respectively. These alterations may compromise patients' ability to direct their attention toward themselves and/or others and to make the decision whether a certain trait applies to one's self or to someone else. In addition, decreased activations were observed in the thalamus, which is not a core region of the default-mode network, and is involved in information integration. These thalamic alterations may compromise self-coherence in schizophrenia.

Keywords: schizophrenia, self-processing, fMRI, meta-analysis, anterior cingulate cortex, prefrontal cortex and thalamus

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INTRODUCTION

Self-disturbances have been described as core phenotypic features of schizophrenia in the early conceptualizations of the disorder (1, 2). More recently, the importance of self-disturbances has been highlighted by phenomenological investigations (3, 4). Self-disturbances in schizophrenia include a lack of insight into the disorder, an impaired ability to evaluate one's own personal qualities, to identify the source of one's own thoughts and actions, as well as the presence of anomalous subjective experiences (e.g., depersonalization and derealization) (4–9). Since self-disturbances are both prominent and diverse in schizophrenia, some investigators now conceptualize schizophrenia as a meta-cognitive disorder (10). Despite this increasing clinical evidence, the neural bases of self-disturbances in schizophrenia are not yet well-understood. This is due to the fact that, on the one hand, the neural correlates of self-processing in healthy individuals have been well-characterized only in the last decade and, on the other hand, until recently there was not yet a critical mass of similar studies conducted in patients with schizophrenia.

The concept of self has been addressed by many disciplines, such as philosophy, psychology, anthropology, psychiatry, cognitive sciences, etc., including by the newcomer to the table: the neurosciences. While there is a debate about its characterization across these disciplines, there is a consensus that the self is a multifaceted construct, with components that seem to correspond to distinct processes (11, 12). Within this framework, a general distinction is made between two aspects of self: the self-experience (i.e., self as an experiencing subject, sense of personal agency, etc.) and self-related processing (i.e., self as object of knowledge, evaluation of one's personal characteristics, self-representation, etc.). The investigation of self and its neural substrates in cognitive neuroscience has mainly focused on the latter aspect, the self-processing or self-referencing, primarily because it is difficult to devise experimental paradigms that would properly isolate the experiencing self in action (usually implicit) from the task demands at hand (usually explicit). As such, in the current review we focused primarily on studies that focused on the self-processing or self-referencing and operationalized it as being the evaluation of information, such as personal traits, adjectives, statements, etc. in terms of being characteristic to "self" (vs. "non-self" or "others").

In healthy participants, the neural correlates of self-processing were mostly investigated using self-referencing or source monitoring tasks. In the self-referencing tasks, participants are typically asked to judge whether certain personality traits describe themselves (Self condition) or a significant person (family member, friend, famous person, etc.) (Other condition). Several meta-analyses that included functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies conducted in healthy participants using self-referencing tasks showed that cortical midline structures, such as the medial prefrontal cortex (PFC), the anterior cingulate cortex (ACC), the posterior cingulate cortex (PCC) and the precuneus, were significantly activated during the Self condition, relative to the baseline condition (i.e., making lexical or semantic judgments) (13–15). In addition to these structures, consistent activations in the anterior insula and temporo-parietal junction (TPJ) were also observed (13, 16, 17). In several literature reviews parsing out the functional roles of some of these brain regions (18–21), the authors proposed that during processing of self-related information, the ACC would be involved in the allocation of attention toward one's self, while the PCC would be involved in the retrieval of autobiographic memory, the (anterior) insula—in the embodiment of self-experiences, the ventro-medial PFC—in the emotional tagging of self-relevant information, and finally, the dorso-medial PFC (dmPFC)—involved in making the decision whether a certain trait applies to one's self or to someone else. In the case of the TPJ (e.g., posterior superior temporal gyrus and ventral areas of the inferior parietal lobule, including the angular gyrus), it is not only involved in self-processing but is also well-known to play a key role in theory of mind (social cognition) (16, 17, 22, 23). As such, the TPJ has been proposed to be a key mediator between self and other perspectives (24, 25). In addition to self-referencing, source monitoring tasks have also been employed to investigate the neural correlates of self-processing in humans, although less frequently. In these tasks, participants are typically asked to determine the particular origin (self vs. other) of a series of stimuli (verbal or visual) that were generated prior to performing the task. In healthy participants, the patterns of activations observed during self-other source monitoring are similar to those observed in studies using self-referencing paradigms. Indeed, activations in cortical midline structures (e.g., mPFC, ACC, and PCC/precuneus) have been consistently observed during (verbal) source monitoring tasks (26, 27). One potential difference between both paradigms is that source monitoring tasks seem to elicit more temporal cortex activations than self-referencing tasks (28).

Converging evidence indicate that the same cortical midline structures (e.g., mPFC, ACC and PCC) reported to be activated during self-referencing and source monitoring tasks also overlap with brain regions that are typically part of the default mode network as identified in resting-state fMRI studies (9, 29, 30). When participants are scanned in task-free conditions (i.e., resting state), it has been consistently shown that the low-frequency fluctuations in spontaneous brain activity of the mPFC, ACC, PCC, and precuneus are positively correlated with each other over time (29, 30). Since participants are presumably involved, at rest, in mind wandering and introspection, the default mode network is conceptualized as the main neural network involved in self-referential processes (30). While there is an overlap in brain activity between regions involved in explicit self-reference (task-elicited) and implicit self-reference (at rest), there are also differences. Indeed, in two experiments comparing both conditions (31), the authors found that implicit and explicit self-reference commonly engaged the ventral mPFC and PCC, while the dorsal mPFC was preferentially recruited during explicit self-reference, and the precuneus, during implicit self-reference.

Recent meta-analyses of the resting-state fMRI literature in schizophrenia have shown that the connectivity within default mode network is reduced in schizophrenia patients as

compared to their healthy counterparts, and, more importantly, that the hypo-connectivity within this network is possibly more prominent in schizophrenia, relative to other psychiatric conditions such as major depressive, bipolar, substance use, and anxiety disorders (32–34).

In contrast to this vast literature on functional connectivity at rest in schizophrenia, it is striking to observe that no meta-analysis has been performed to date on studies investigating the self-related brain activations in this population. Whereas, resting-state fMRI studies are advantageous in that they are more simple to implement by circumventing the problem of task design optimization, classic task-based activation studies are advantageous in that they allow to relate more directly fMRI findings to psychological constructs. However, only in recent years the number of fMRI studies conducted in schizophrenia patients using self-processing tasks have reached the critical mass needed for a meta-analysis on this topic [e.g., (5, 35–40)]. At first glance, these studies have reported abnormal activations during self-processing in schizophrenia in the same cortical midline structures that are typically found in healthy participants; however, the pattern of results is not always consistent since most studies showed reduced activations (patients vs. controls), but a few reported the opposite result. Moreover, altered activations have been reported in some cases in regions unrelated to the default mode network (e.g., insula, temporal cortex, and thalamus), but their significance remains unclear at the moment. Given this heterogeneity and these particularities, a meta-analysis on the neural bases of self-processing in schizophrenia relative to healthy controls is critically needed.

Here, we sought to address this knowledge gap and perform a functional neuroimaging meta-analysis on self-processing in schizophrenia. Given that schizophrenia is associated with self-disturbances, that self-processing tasks recruit activations in cortical midline structures and that the connectivity within the default mode network is reduced in schizophrenia, we hypothesized that decreased activations in cortical midline structures and the TPJ will be observed in schizophrenia patients, relative to healthy participants.

METHODS

Selection Procedures: Search Strategies

The article search was conducted by two researchers (SP and OL), independently, using PubMed, Google Scholar and Web of Science databases. The search used the following syntax [schizophrenia AND (self OR self-reference OR insight) AND (fMRI OR neuroimaging OR functional magnetic resonance imaging)] and was limited to all original articles (i.e., excluding abstracts from conference proceedings) published before September 20, 2018. It is worth noting that the search syntax is very general and it does not exclude, *a priori*, studies that may investigate self-agency. However, as stated previously, our goal is to identify studies that assessed the functional brain activity underlying the self-processing or self-referencing (and not necessarily the self-agency or the experiencing self) in schizophrenia. A cross-referencing method was also used by manually examining reference lists of the articles included in the meta-analysis.

Selection Criteria

Studies were included in the meta-analysis provided that they met the following criteria: (i) included a self-reference, self-other distinction, memory source (i.e., self-generated) or insight task (and not self-agency), (ii) contained primary data, (iii) included both psychosis participants (e.g., patients with a diagnosis of schizophrenia-spectrum or psychotic disorder, or participants at risk of psychosis) and a healthy control group and (iv) compared directly the brain activation of these two groups in experimental conditions that included reference to self. Studies were reviewed by two researchers (OL, SP) and inclusion criteria were evaluated by consensus. To achieve a high reporting standard, we followed the "*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*" (PRISMA) guidelines (41) (for more information, see **Table 1**).

Recorded Variables

The variables included in the present meta-analysis, for each article, were: sample size, mean age of patients, antipsychotic dosage (e.g., chlorpromazine equivalents), level of psychiatric symptoms, magnet intensity, voxel size, and repetition time (TR) of functional volumes. Smoothing kernel size was also recorded in the meta-analysis, as recent research has shown this preprocessing parameter is a source of heterogeneity of results in neuroimaging studies (49).

Meta-Analysis

The meta-analysis was performed using the *Effect-size Seed-based d Mapping* (formerly *Signed Differential Mapping*) (ES-SDM) software (50). The voxel-based approach of ES-SDM is based on the use of *t*-values of peak coordinates to recreate, for each study, an effect-size map of contrast results. To do so, we first extracted peak coordinates and t-statistics of clusters showing significant differences in brain activity at the whole-brain level between schizophrenia patients and healthy volunteers. Both the "schizophrenia > controls" and "controls > schizophrenia" contrasts were used. When the authors reported z-scores instead of t-statistics, these were converted to *t*-values using the t-calculator provided by ES-SDM (http://www.sdmproject.com/utilities/?show=Statistics). Coordinates presented in Talairach space were converted to Montreal Neurological Institute (MNI) space during analysis in ES-SDM. Importantly, studies reporting no statistically significant between-group differences were also included in the meta-analysis. Finally, effect-size brain maps were created by means of an anisotropic Gaussian kernel. Studies were then combined using a random effects model, which takes into account sample size and heterogeneity across studies. Default ES-SDM kernel size and thresholds were used (FWHM = 20 mm, voxel $P = 0.005$, peak height $Z = 1$, cluster extent = 10 voxels) (50).

Robustness of the significant results was assessed by means of exploration of the residual heterogeneity, jack-knife, and subgroup analyses. Publication bias were assessed by examining

TABLE 1 | Description of studies included in the meta-analysis ($N = 14$).

References	N patient group	N healthy controls	Mean age patients	Mean age controls	Type of analysis	Type of task	Task modality	Software	Magnetic field strength	Smoothing (FWHM)	TR
Bedford et al. (42)	11	8	39.0	31.0	WB	Trait judgement	Visual - W	XBAM	1.5	8	2,000
Blackwood et al. (35)	8	8	38.0	36.0	WB	Statement judgement	Visual - W	SPM99	1.5	10	3,000
Holt et al. (36)	18	17	35.9	40.0	WB	Trait judgement	Visual - W	SPM2	3	6	3,000
Jimenez et al. (43)	20	16	48.3	44.7	WB	Trait judgement	Visual - W	FSL	3	5	2,500
Liu et al. (5)	15	15	50.0	40.5	WB	Self-referential task	Visual - W	SPM	3	6	1,500
Makowski et al. (44)	15	15	33.1	35.2	WB	Social approval task	Visual - W	SPM8	3	8	2,000
Menon et al. (37)	14	15	40.5	35.9	WB and ROI	Statement judgement	Visual - W	SPM5	1.5	8	2,300
Murphy et al. (45)	11	10	26.7	29.6	WB	Trait judgement	Visual - W	SPM2	4	6	2,000
Park et al. (46)	14	15	29.5	28.2	WB	Self-referential task	Visual - V	AFNI	1.5	8	3,000
Pauly et al. (39)	13	13	36.2	34.5	WB	Trait judgement	Visual - W	SPM5	3	8	2,400
Sapara et al. (38)	26	16	34.5	31.8	WB	Self-monitoring	Auditory	SPM	1.5	10	3,250
Shad et al. (47)	17	15	40.0	44.3	WB	Self-awareness	Visual - W	SPM5	3	8	2,000
Tan et al. (48)	18	17	40.5	41.2	WB	Trait judgement	Visual - W	SPM8	2	8	3,000
van der Meer et al. (40)	47	21	34.3	30.0	WB	Statement judgement	Visual - W	SPM2	3	10	2,000

WB, whole brain; ROI, region-of-interest. Task modality: visual (visual stimuli, usually words—W or videos—V, presented on the screen), auditory (auditory stimuli, usually speech, presented binaurally).

Egger's test (51) for asymmetry of the funnel plots (52). Jackknife sensitivity analyses consisted of repeating the meta-analysis iteratively by removing one study at a time to assess the replicability of the results (50). Subgroup analyses were conducted on task contrast (self vs. control; self vs. other) as well as on the smoothing kernel used (5–10 mm^3). Finally, a meta-regression was performed on mean age of patients, voxel size and TR across studies. The influence of antipsychotic dosage and psychiatric symptoms could not be assessed, as data was available in fewer than 10 studies. Following previous meta-analyses, we increased the probability threshold to minimize the detection of spurious results [see (50) and (53) for further details on robustness analyses].

RESULTS

Number of Studies Retrieved

After removing duplicates, the initial search yielded 884 articles (as of 20 September, 2018). Of these, 20 studies met the inclusion criteria (i), (ii), and (iv). Of this group, 4 studies were further excluded because it involved individuals at risk for psychosis and not actual patients, and one other study was excluded (54) because it seemed to report data on the same healthy control group and a sub-sample of schizophrenia patients that was included in a previous study, already included in the selection (55). In the course of data analysis, the study from Vinogradov et al. (56) was also excluded, due to its outlier results (defined as 2 standard deviations above or below the composite effect size). A total of 14 studies were included in the final meta-analysis (5, 35–40, 42–48) (see **Figure 1** for the flow chart), which comprised a total of 245 schizophrenia-spectrum patients (mean age: 37.5 year) and 201 healthy volunteers. Noteworthy, all included studies used a whole-brain analysis. Eight studies reported results for the Self vs. Other contrast, 4 studies reported results for the Self vs. Control contrast and two studies reported results for both contrasts. Thus, the Self vs. Other contrast results are based on data from 10 studies and those for Self vs. Control—on data from 6 studies. The weighted mean of symptoms level, as measured with the *Positive and Negative Syndrome Scale* total score, was 61.9 ± 10 ($n = 8$ studies). Please refer to **Table 1** for details on the included studies.

Between-Group Differences in Brain Activations

For the composite analysis (14 studies), we found that schizophrenia patients had *decreased* activations, relative to controls, in a cluster encompassing the left medial superior frontal gyrus, the left ACC, the bilateral median cingulate cortex, the right superior frontal gyrus, and another cluster encompassing the bilateral thalamus. For these reduced activations in schizophrenia, we observed no significant residual heterogeneity between studies ($\tau = 0.0$; $Q = 9.1$; $p = 0.521$). There were no significant *increased* activations in schizophrenia patients as compared to controls for this analysis (**Table 2**, **Figure 2**).

The analyses of robustness (Jacknife analyses) revealed that results were highly replicable since the reduced activations in

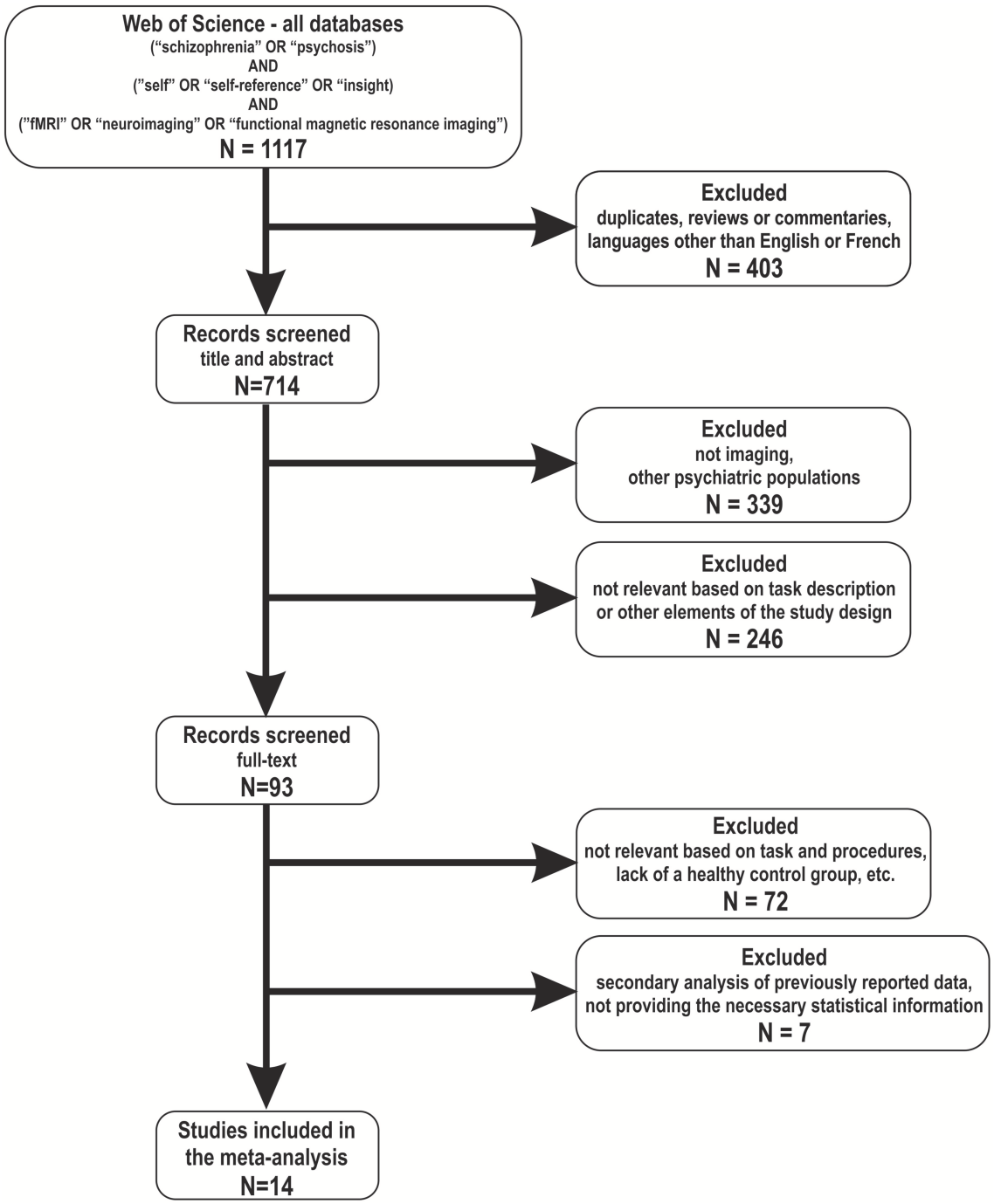

FIGURE 1 | Flow chart of the articles included in the meta-analysis.

schizophrenia in the left thalamic cluster were found in 100% of studies, while the reduced activations in schizophrenia in the left anterior cingulate cluster were found in 92.9% of studies (**Table 3**).

Finally, in the case of both clusters, no publication bias was detected (left ACC: bias $= -1.54$; $t = -1.27$; $df = 13$; $p = 0.227$; left thalamus: bias $= -1.62$; $t = -0.97$; $df = 13$; $p = 0.351$).

Meta-Regression Sub-analyses

Using the data from the composite analysis, we found no association between results in the ACC across studies and age (slope $= 0.002$; $z = 0.101$; $p = 0.920$), temporal resolution (TR; slope $= 0.00004$; $z = 0.226$; $p = 0.821$), spatial resolution (voxel size; slope $= -0.004$; $z = -0.726$; $p = 0.468$), and smoothing level (slope $= -0.02$; $z = -0.184$; $p = 0.854$). Likewise, thalamic

TABLE 2 | Meta-analysis of brain activations during self-processing in schizophrenia patients relative to controls.

Region (peak)	MNI coordinates	*Z*-value	*P*-value	No of Voxels	Breakdown (number of voxels)**
COMPOSITE ANALYSIS*					
Left anterior cingulate cortex (BA32)	−2; 32; 30	−1.2	0.0009	562	- Left medial superior frontal gyrus (BA32/8, 149), left anterior cingulate cortex (BA24/32, 160), left median cingulate cortex (BA24, 62), right median cingulate cortex (BA32/24, 77), and right superior frontal gyrus (BA32, 24)
Left thalamus	−8; −26; 10	−1.6	∼0	265	- Left thalamus (140), and right thalamus (49)
SELF vs. OTHER CONTRAST					
Left anterior cingulate cortex (BA32)	−2; 40; 26	−1.4	0.0004	1,073	- Left medial superior frontal gyrus (BA32/9/8, 526), right superior frontal gyrus (BA9, 81), left anterior cingulate gyrus (BA32/24, 153), right median cingulate gyrus (BA32, 54), left median cingulate gyrus (BA24, 44), right anterior cingulate (BA32, 39), and right median cingulate gyrus (BA24, 33)
Left inferior temporal gyrus (BA37)	−48; −46; −28	−1.3	0.001	355	- Left cerebellum, crus I (BA37, 132), left inferior temporal gyrus (BA20/37, 118), left cerebellum, hemispheric lobule VI (BA37, 51), and left fusiform gyrus (BA37, 31)
Right angular gyrus (BA39)	46; −64; 40	−1.2	0.002	205	- Right angular gyrus (BA39/7, 184)
SELF vs. CONTROL (OR BASELINE) CONTRAST					
Left thalamus	−8; −28; 10	−1.9	0.00005	573	- Left thalamus (292), and right thalamus (133)
Left anterior cingulate cortex (BA24)	−8; 26; 22	−1.5	0.0005	257	- Left anterior cingulate gyrus (BA24/32, 168)

*BA, Brodmann area; MNI, Montreal Neurologic Institute. *Two studies reported results for both the Self vs. Other and the Self vs. Control contrasts; in these two cases, for the composite analysis, we used the self vs. other contrast, as it was the most frequently employed in the set of studies included in the meta-analysis; ** >20 voxels.*

results across studies were not influenced by age (slope:0.018; $z = 1.138$; $p = 0.255$), temporal resolution (TR; slope $= -0.0004$; $z = -2.341$; $p = 0.019$), spatial resolution (voxel size; slope $= -0.003$; $z = -0.471$; $p = 0.638$) and smoothing level (slope $= -0.099$; $z = -1.693$; $p = 0.091$).

Task Contrasts

For the analysis restricted to the Self vs. Other contrast (10 studies), we found that schizophrenia patients had *decreased* activations, relative to controls, in the left medial superior frontal gyrus, the right superior frontal gyrus, the bilateral ACC, the bilateral median cingulate cortex, the left cerebellum (crus I & hemispheric lobule VI), the left inferior temporal gyrus, the left fusiform gyrus, and the right angular gyrus (**Table 2**). For this pattern of hypo-activations in schizophrenia, we observed no significant residual heterogeneity between studies ($\tau = 0.0$; $Q = 2.6$; $p = 0.765$). As before, we did not find any significant *increased* activation in schizophrenia relative to controls (**Table 2**).

For the analysis restricted to the Self vs. Control (or baseline) contrast (6 studies), we found significant *decreased* activations in schizophrenia patients relative to controls in the bilateral thalamus, and left ACC (**Table 2**). There was no significant residual heterogeneity between studies ($\tau = 0.0$; $Q = 2.0$; $p = 0.918$) in regards to this result. Again, schizophrenia patients had no *increased* activations relative to controls (**Table 2**).

DISCUSSION

To our knowledge, this is the first functional neuroimaging meta-analysis to examine the neural correlates of self-processing in schizophrenia. Fourteen studies were retrieved, and the aggregation of their results showed that activations in the dorsal anterior cingulate cortex (dACC), the dorsomedial prefrontal cortex (dmPFC) and the thalamus display reduced activations in schizophrenia patients, relative to healthy participants, during self-processing. Importantly, the results of the meta-analysis were homogeneous and robust, and were not influenced by publication biases. In secondary analyses, we found that patients' age, as well as neuroimaging parameters (e.g., temporal resolution, spatial resolution, and smoothing level) had no influence on results.

Comparing our findings with those reported in the previous meta-analyses on the neural bases of self-processing in healthy individuals (13–15) we observe that, on the one hand, we have found hypo-activations only in a core node region involved in self-referential processing in healthy controls (dmPFC) and in a region involved in cognitive control and/or salience attribution (e.g., dACC) and, on the other hand, we have localized a group difference in a subcortical region outside the typical self-processing network (thalamus). Considering that all 14 studies included in the current meta-analysis reported results of brain-wise contrasts (i.e., not restricted to previously reported regions of interest), the localization of the hypo-activations in two of the self-referential midline cortical structures indicate a high construct validity. Moreover, given the critical role of thalamus as a gateway relaying of sensory and motor information, and regulating consciousness, mood, sleep and alertness (57–60), the reduced activation found in this region is consistent with the recently proposed view that self-related impairments seen in schizophrenia patients may be a reflection of a fragmented self, due to the isolation and reduced modularity of brain networks involved in intrinsic and extrinsic self-processing (9).

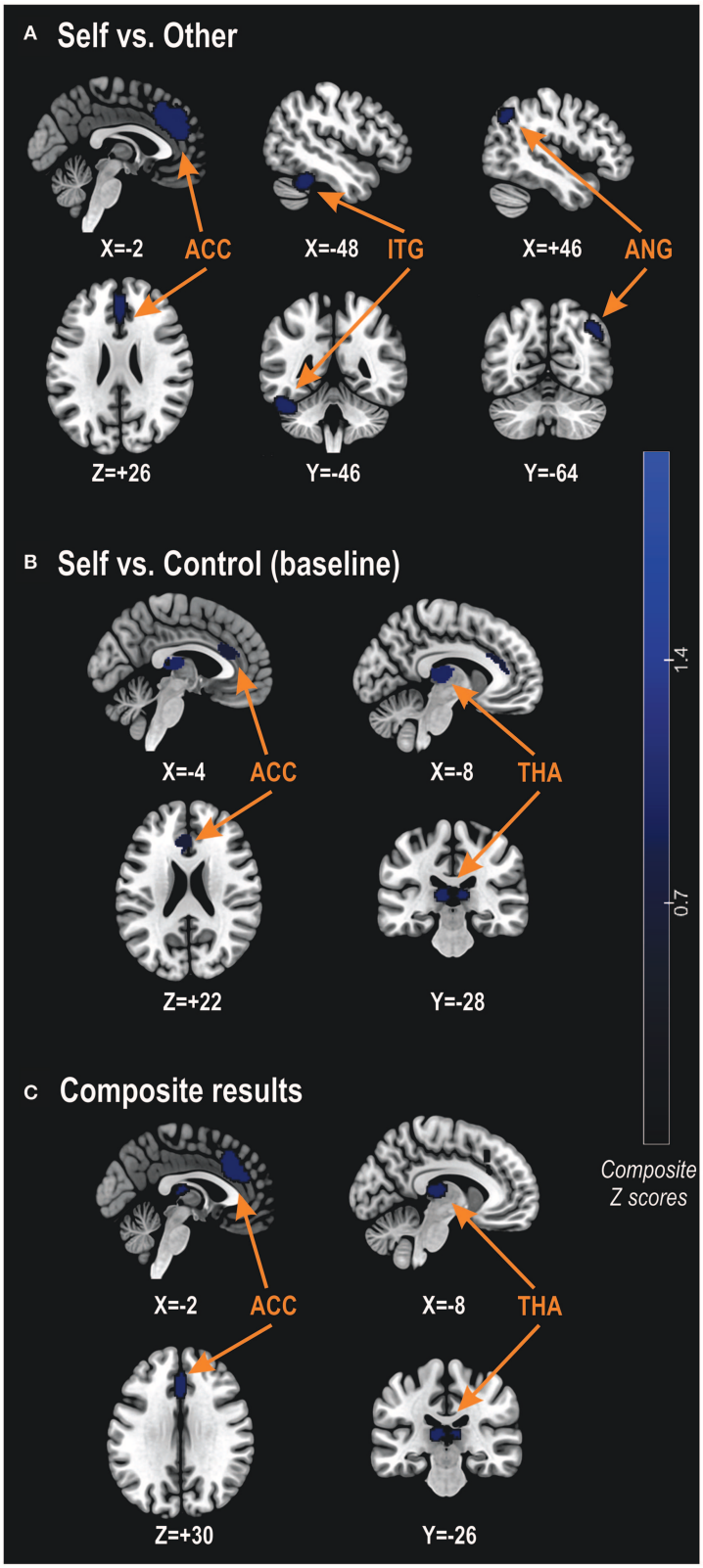

FIGURE 2 | Between-group differences in self-related brain activations. **(A)** Results for the between-group differences in brain activations using the Self vs. Other contrast. **(B)** Results using the Self vs. Control (baseline) contrast. **(C)** Results for the composite analysis, combining every studies including in the meta-analysis. ACC, anterior cingulate cortex; ANG, angular gyrus; ITG, inferior temporal gyrus; THA, thalamus.

TABLE 3 | Jacknife analyses.

Jacknife analysis	Reduced activations in schizophrenia	
	Anterior cingulate cortex	Thalamus
Without Bedford et al. (42)	Yes	Yes
Without Blackwood et al. (35)	Yes	Yes
Without Holt et al. (36)	Yes	Yes
Without Jimenez et al. (43)	Yes	Yes
Without Liu et al. (5)	Yes	Yes
Without Makowski et al. (42)	Yes	Yes
Without Menon et al. (37)	*No*	Yes
Without Murphy et al. (45)	Yes	Yes
Without Park et al. (46)	Yes	Yes
Without Pauly et al. (39)	Yes	Yes
Without Sapara et al. (38)	Yes	Yes
Without Shad et al. (47)	Yes	Yes
Without Tan et al. (48)	Yes	Yes
Without Van der Meer et al. (40)	Yes	Yes
Total	**13/14**	**14/14**

Given that the dACC and dmPFC are core cortical midline structures, the reduced activations found in these regions in schizophrenia provide support for the main hypothesis that we sought to test in the current meta-analysis. The dACC is inter-connected with frontal, striatal, and limbic regions, and its roles are complex and matter to debate. Nevertheless, there is ample evidence from task-based fMRI studies showing that the dACC and the adjacent median cingulate cortex play a key role in cognitive control and attention (21, 61). In complementary fashion, a vast resting-state functional connectivity literature has shown that the dACC is one of two core nodes of the salience network (the other being the anterior insula) (62, 63). In schizophrenia, several studies have shown that the connectivity between the dACC and the anterior insula is reduced (33). In theory, it has been proposed that the salience network is involved in the orientation of attention to the most salient internal and external stimuli. Accordingly, it may be argued that the reduced dACC activations observed in schizophrenia patients may compromise their ability to allocate or shift their attention toward themselves and/or others. As for the dmPFC, Van der Meer et al. (13) proposed in their model that this region would be involved in the *decision making* processes involved in self-referencing tasks. If so, the reduced dmPFC activations observed in schizophrenia may indicate that these patients experience difficulties in deciding whether a certain personality trait applies to one's self or to someone else. However, the results of a recent neuroimaging meta-analysis from Eickhoff et al. of fMRI studies performed in healthy participants on the roles of the dmPFC suggest that a slightly different interpretation of our results is possible (64). Indeed, this meta-analysis has highlighted that the dmPFC and the PCC are significantly co-activated, and that the dmPFC plays a key role in social cognition, noticeably *theory of mind* (64). The results of the meta-analysis from Eickhoff et al. (64) suggest that the reduced dmPFC activations observed in schizophrenia may not reflect impaired decision making abilities *per se*, but rather a difficulty in attributing mental states to others. Interestingly, in the current meta-analysis, we found that the dmPFC activity was reduced in schizophrenia only in the fMRI studies using a "self vs. other" contrast, whereas the studies using a "self vs. control/baseline" contrast showed no between-group differences in dmPFC activity. In that regard, it is interesting to note that a neuroimaging meta-analysis from Kronbichler et al. on social cognition showed that schizophrenia patients have reduced dmPFC activations while performing theory of mind tasks (65).

While the reduced dACC and dmPFC activations found in schizophrenia during self-processing are generally consistent with main hypothesis of the current meta-analysis, we also found that schizophrenia patients had reduced activations in the thalamus, which is not considered a cortical midline structure, but rather being part of a network involved in information gating (33) or as part of the salience network (cortico-striato-thalamo-cortical)—the mediodorsal thalamus (66). This finding is particularly novel in that the vast majority of investigators who performed the fMRI studies on self-processing in schizophrenia in the current meta-analysis highlighted the importance of alterations in cortical midline structures (5, 36, 37, 39, 40, 42–45, 47, 48). Conversely, we are not aware of any investigator who discussed the importance of the thalamus, meaning that the role of this region has clearly been neglected thus far. Noteworthy, thalamic activity was found to be decreased only in studies using a "self vs. baseline/control" task contrast. The thalamus is massively interconnected with the whole cerebral cortex, the cerebellum, and is involved in information integration from every sensory system (67), information gating (33), as well as in awakening and consciousness (68). As such, the thalamic alterations found in schizophrenia during self-processing are possibly indicative of a lack of self-coherence. The observed thalamic alterations observed here are coherent with the fact that the thalamus is growingly considered as being critically involved in the pathophysiology of schizophrenia. Indeed, data from the ENIGMA consortium has shown in 2,028 schizophrenia patients and 2,540 healthy controls that schizophrenia is associated with a small to moderate ($d = 0.31$) decrease in thalamic volumes (69). Likewise, several resting-state functional connectivity studies have shown that the connectivity between the thalamus and frontal, cingulate, sensorimotor, and cerebellar regions is significantly reduced in schizophrenia (70, 71). Perhaps more importantly, a recent multi-modal neuroimaging meta-analysis of resting-state functional connectivity studies and voxel-based morphometry studies showed that among all the regions found to be impaired in schizophrenia patients relative to healthy controls, the thalamus was one of the few regions found to be not only reduced in volumes, but more prominently impaired in its functional connectivity in schizophrenia patients, relative to patients with bipolar, major depressive, substance use and anxiety disorders (32).

Apart from the dmPFC, dACC, and thalamus, other regions were found to be significantly impaired in schizophrenia during

self-processing. Noticeably, reduced activations in the right angular gyrus were observed in schizophrenia patients relative to controls. In addition to the cortical midline structures (e.g., mPFC, ACC, PCC, and precuneus), the angular gyrus is one of the core regions of the default mode network (29, 30). The right angular gyrus is part of the TPJ and is involved in several functions, including self-processing, spatial cognition, attention, and theory of mind (17, 22). The involvement of the right angular gyrus in theory of mind is of particular interest in the current context. Indeed, the reduced activations observed in this brain region in schizophrenia were only observed in the case of the studies using a "self vs. other" contrast, but not in the studies using a "self vs. baseline/control" contrast. This result is consistent with the notion that the TPJ is involved the mediation between self and other perspectives. As such, the result suggests that self/other differentiation is impaired in schizophrenia, and the TPJ is involved in this impairment. Finally, in the studies using a "self vs. other" contrast, reduced activations were also observed in schizophrenia in a cluster encompassing the left inferior temporal cortex, fusiform gyrus, and cerebellum. While the inferior temporal cortex is involved in color, face and object recognition, and semantic memory, the fusiform gyrus is involved in face and object recognition and reading, and the cerebellum crus I is primarily involved in higher cognitive functions (72–74). In view of these heterogeneous functions, it is difficult to interpret the reduced activations observed in this cluster in schizophrenia during self-processing. However, two of these regions (inferior temporal cortex and fusiform gyrus) are located along the inferior longitudinal fasciculus and are part of the ventral visual stream. Previous studies have shown that the integrity of the inferior longitudinal fasciculus was associated with semantic (as opposed to episodic) autobiographical memory (75), that ventral stream increased activation was associated with successful encoding of emotional information (76). In light of these previous findings, our results could be interpreted as a functional deficit in the processing of emotional autobiographical memories in schizophrenia patients. The fact that the cluster included also the left Crus I/lobule VI of the cerebellum strengthens this interpretation. Indeed, a quantitative review of cerebellar findings in fMRI literature reported not only that cerebellar hypoactivations predominate across studies and various tasks in schizophrenia, but that emotional tasks yielded results in the left lobule VI (77).

In recent years, there is increasing evidence that the cerebellum plays a broader role in cognition than previously thought (78), thus challenging the traditional view that it is primarily involved in motor control (79). Indeed, a recent review of neuroimaging and clinical studies highlights the cerebellar involvement in performance monitoring across a variety of domains and tasks (80) and suggesting that monitoring may be cerebellum's "overarching function" (81). This view is consistent with the findings from recent meta-analyses on the role of cerebellum in social cognition, which identified "mentalizing networks" within the cerebellum that are active when people engage in self-judgement or self-processing tasks (82–84). Given the findings from the meta-analysis by Van Overwalle et al. (82) that have identified activation clusters in left lobule VI when mentalizing about distant others and activation in Crus I when performing abstract mentalizing tasks, the cerebellar hypoactivation in these regions in our meta-analysis seems to indicate that the deficit in these kind of self-processing tasks in schizophrenia may be due to the malfunctioning of these mentalizing networks. As such, the cognitive dysmetria hypothesis in schizophrenia and its cerebellar substrate may be expanded to include self-processing.

The current meta-analysis suffers from a few limitations that need to be acknowledged. First, schizophrenia patients were treated with antipsychotics at the moment of being scanned, meaning that we cannot determine if our results are related to schizophrenia, to antipsychotic medication and/or to a combination of both factors. Antipsychotics are known for blocking dopamine release in the associative striatum (85). Other than that, the impacts of antipsychotics on brain structure and function remain unclear. Thus far, the majority of studies have paid attention to the anatomical effects of antipsychotics (86). As for the fMRI studies, the available evidence tends to show that antipsychotics *normalize*, rather than impair, task-based activations and resting-state functional connectivity in schizophrenia (87). Moreover, little evidence shows that antipsychotics have beneficial effects particularly on the functioning of the brain regions of the default mode network (87). Still, in the pool of studies included in our meta-analysis, not enough of them reported the mean antipsychotic dosage (e.g., chlorpromazine equivalents) of patients, so we were not able to perform a meta-regression analysis, which would have allowed to investigate the potential influence of antipsychotic medication on the abnormal activations observed in schizophrenia during self-processing. Likewise, not enough studies reported the level of symptoms of patients to perform meta-regression analyses. In the past, some authors proposed that self-disturbances in schizophrenia may be related to the positive symptoms of the disorder (6), while others proposed that the lack of insight of some patients is due to self-disturbances (38). Unfortunately, in the current meta-analysis, we were not able to examine both possibilities. Moreover, there were not enough studies to perform sub-analyses on the type of task used in the scanner (e.g., trait judgment vs. source monitoring). Also, we did not contact authors, so statistical maps were not used for analysis, and this may have limited statistical power. Finally, we were not able to include the studies involving individuals at risk for psychosis in the meta-analytic analyses, since only 4 studies were identified, despite the fact that heterogeneous definitions of psychosis risk were considered (e.g., schizotypy, first-degree relatives, siblings) (88–91). Thus far, 3 of these studies have shown altered activations in cortical midline structures (e.g., dmPFC and PCC) during self-processing in individuals at risk for psychosis relative to typically developing individuals.

The current results partially support the hypothesized impaired activity of cortical midline structures in schizophrenia during self-processing. Indeed, decreased activations were observed not only in cortical midline structures (e.g., dACC and dmPFC), but also in the thalamus, which is not a core region of the default-mode network. Taken together, the results

of the current meta-analysis suggest that self-disturbances in schizophrenia are related to decreased activity in brain regions involved in attention and/or salience attribution (e.g., dACC), decision-making and/or theory of mind (e.g., dmPFC), as well as experiential coherence (e.g., thalamus). Future enquiries in the field will need to combine analyses of resting-state functional connectivity and analyses of task-based activations, as they provide complementary information. An important issue will be to investigate the functional connectivity between the default-mode and salience networks during explicit self-processing in schizophrenia, similar to the emerging investigations on the interactions between these networks at rest in this population (92). In the future studies on the topic, careful attention will need to be paid to the potential impact of antipsychotic medication. Finally, more studies are warranted on the neural alterations associated with self-disturbances in individuals at clinical or biological risk for psychosis.

AUTHOR CONTRIBUTIONS

SP conceived the idea of the study, did the search of studies, performed the meta-analytic statistics, and wrote the manuscript. OL did the search of studies, performed the data extraction, prepared the tables and figures, and wrote the manuscript. LG was involved in the study selection, did the data extraction, prepared the tables and figures, prepared the references, and provided the detailed critical comments. All authors approved the final version of the manuscript.

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CASE REPORT
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A Multimodal Imaging Study in a Case of Bilateral Thalamic Damage With Multidomain Cognitive Impairment

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Severe thalamic injury can determine a particular type of vascular dementia affecting multiple network dysfunctions, considered the central role of thalamus as a hub for afferent and efferent stimuli. A 67-year-old male patient with bilateral thalamic stroke was studied with positron emission tomography, magnetic resonance imaging, and cognitive assessment, performed at baseline and at two follow-up evaluations. A pattern primarily involving thalamo-frontal connections was observed by both PET and tractography analyses. All significant differences between the patient and controls involved the anterior thalamic radiation, one of the major fiber tracts in the fronto-thalamic circuitry. In particular, altered tractography indices of higher radial diffusivity and apparent diffusion coefficient and reduced fractional anisotropy values for the anterior thalamic radiation were reported. In accordance with imaging findings, neuropsychological evaluation demonstrated a multidomain impairment including memory, executive functions, and attention. Additionally, the patients displayed behavioral symptoms, in absence of mood alterations. Multimodal imaging assessment, revealing the metabolic and microstructural alterations that attend to multidomain neuropsychological impairment, demonstrated multiple levels of adaptations to bilateral vascular thalamic injury.

Keywords: thalamus, stroke, PET, MRI, dementia, connectivity

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INTRODUCTION

The thalamus is the core diencephalic brain structure subdivided into several nuclei having wide bidirectional connections with cortical and subcortical regions, e.g., cingulate cortex, hippocampus, and amygdala (1). Each portion of the thalamus has specialized connections and functions. Its anterior part receives projections from the mammillo-thalamic tract and is mainly linked with orbitofrontal cortex and cingulate cortex; it is principally involved in memory and emotional disorders. The paramedian nuclei connect with amygdala, prefrontal cortex, globus pallidus, and motor and premotor cortex; its stroke causes reduced consciousness, disinhibition, apathy, and amnesia. The inferolateral territory is responsible for executive functions whereas the posterior portion has projections to occipito-parietal, prefrontal, cingulate, and parahippocampal cortices; no particular behavioral alterations are reported if specifically injured, whereas some cognitive deficits have been described (2).

Literature describes several cases of patients presenting thalamus lesion often affected by cognitive, emotional, and motor deficits; aphasia, agnosia, amnesia, and neglect also occur after thalamic stroke (3–5).

Stenset et al. (6) described a 67-year-old patient with left thalamic lesion who suffered of memory dysfunction; the ^{18}fluorodeoxiglucose positron emission tomography (PET) evidenced reduced metabolism in the left anterior thalamus and in frontal, parietal, and temporal lobes in the left hemisphere. Magnetic resonance imaging (MRI) also showed a lesion in the left anteromedian portion of the thalamus.

Differently, Shim et al. (4) used single photon emission computerized tomography (SPECT) and MRI for studying four patients with focal left thalamus stroke, who reported executive dysfunctions in addition to memory impairment. They also found decreased regional cerebral blood flow in frontal, parietal, and temporal gyri and MRI revealed disruption of fibers in the infarcted thalamic area.

Later, SPECT used on 18 patients with left thalamic lesion showed that reduced perfusion observed in both the hemispheres correlated with deficit in executive functions and depression state (5).

More recently, Song et al. (7) described a case report of a thalamic infarction due to artery of Percheron occlusion who presented speech and behavioral alterations.

As shown, available studies in literature used various approach for studying thalamic lesions. It seems that there does not exist a general consensus about methods to perform; therefore, the results are also heterogeneous. Overall, in all cases, thalamic infarct was accompanied by diffuse brain metabolism alterations, and cognitive complaints differed according to lesion site and extension.

In the present study, we examined one patient presenting with bilateral thalamic lesions that we evaluated three times: at baseline (T0) and after 6 months (T1) and 18 months (T2). During the same session, brain PET-CT and MRI were performed with an advanced imaging protocol that includes diffusion tractography (DT).

In addition, neuropsychological assessment to investigate cognitive dysfunctions complained by the patient was performed.

MATERIALS AND METHODS

Case Description

A 67-year-old male patient was admitted to undergo a brain PET-CT and MR for investigating amnestic symptoms he manifested. He referred focal brain hemorrhage in the left superior temporal gyrus in 2016; he complained about memory dysfunctions and visual hallucinations; he also had a persistent left leg pain that makes walking difficult. He was fully cooperative and denied his cognitive problems.

The first PET-CT and MR results (T0) revealed thalamus lesions; therefore, we decided to evaluate the patient, with the same imaging protocol, in two follow-up times, after 6 months (T1) and after 18 months (T2) from injury. Additional MRI exam with contrast agent injection was performed to exclude tumor pathology at baseline. Furthermore, 13 healthy volunteers matched for gender, age, Fazekas score [in regions different from the thalami; (8)], and white matter lesion load (9) (13 males; mean age: 69.31 $\pm$ 3.12; total volume lesion: 2.17 $\pm$ 1.64), performing the same MR protocol, were selected as the control group.

Clinical and Neuropsychological Assessment

The patient performed cognitive tests and clinical scales at the baseline evaluation and at the second follow-up time. The global cognitive status was assessed with the Mini Mental State Examination [MMSE; (10)], the Montreal Cognitive Assessment [MoCA; (11)], and the Frontal Assessment Battery [FAB; (12)]. The Clinical Dementia Rating Scale [CDR; (13)] was used to evaluate the degree of dementia severity; it ranges from no dementia (0) to severe dementia (3). Memory is considered the major domain from which they depend subsequent cognitive domain scores depend on orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The patient also performed Raven's colored progressive matrices (14), phonological and semantic verbal fluency (15, 16), Stroop test (17), Milan constructional apraxia (18), and trail making test (19) in order to collect a comprehensive cognitive profile.

We investigated neuropsychiatric symptoms as depression with the Beck Depression Inventory-II (20), behavioral disorders with the Frontal Behavior Inventory (21), apathy with the Apathy Evaluation Scale (22), and interoceptive consciousness with the Self-Awareness Questionnaire [SAQ; (23)].

Positron Emission Tomography–Computerized Tomography

Data were acquired using a Discovery 710 PET-CT scanner (GE Healthcare), according to European guidelines (24). The subject was intravenously (i.v.) injected with 250 MBq of [18F]-FDG dose, after a resting period (15 min) in a quiet and dark room. Following the radiotracer injection uptake period of 20–25 min, during which the patient rested with eyes closed, PET data were acquired in sinogram mode for 10 min; matrix size was 256 $\times$ 256. PET emission data were reconstructed with ordered subset-expectation maximization (OSEM) algorithm (21 subsets, 4 iterations) and post-filtered with a three-dimensional isotropic gaussian of 4 mm at FWHM. Attenuation correction was performed using CT-based attenuation maps derived from a CT scan (140 kV, 300 mA, 3.75 mm thickness).

Magnetic Resonance Imaging

In the same day, a 3-T Biograph mMR tomograph (Siemens Healthcare, Erlangen, Germany) was used, equipped with a 12-channel head coil, after 1 h from radiotracer administration. The MRI protocol included morphological volumetric T1 (TR: 2,400, TE: 2.25, voxel: 0.8 mm^3 isotropic, matrix: 256 $\times$ 256), T2 (TR: 3,370, TE: 563, voxel: 0.8 mm^3 isotropic, matrix: 256 $\times$ 256), Fluid Attenuated Inversion Recovery (TR: 5,000, TE: 354, voxel: 1 mm^3 isotropic, matrix: 192 $\times$ 192) as well as techniques like DTI (TR: 3,851, TE: 84.2 voxel: 2 mm^3 isotropic; 71 directions; *b* value max: 1,500, matrix: 128 $\times$ 128). Foam wedges were used to minimize movement artifacts, and the patient held eyes closed during the resting-state scan.

Image Analysis

PET-CT

PET images were processed with Scenium tool, of Syngo.Via software (Siemens Healthcare, Erlangen, Germany). It normalized and parceled with a standardized PET database of healthy subject matched for age [Database: FDG-PET Biograph HD, age 46–79, Cerebellum-Vermis; Atlas: Automated Anatomical Labeling; (25)].

DT

White matter lesions were segmented by the lesion prediction algorithm (9) as implemented in the LST toolbox version 2.0.15 for Statistical Parametric Mapping 12 (SPM12).

The diffusion tensor images were elaborated with software FSL and MrTrix by the following processing steps: denoizing (26), motion and eddy current correction (27), DWI reslicing to the T1 space by trilinear interpolation (28), ACT (anatomical–constrained tractography) (29), and deterministic tractography reconstruction (30).

Anterior thalamic radiation segmentation, between thalamus and homolateral frontal cortex, was performed by TrackVis (Version 0.6.1) on control group and on each patient's time points. A volume of interest (VOI) on thalami and a region of interest (ROI) on frontal region were applied to reconstruct anterior thalamic radiation. Thalamus VOIs were defined by considering the segmentation of subcortical areas resulting from standard FreeSurfer (v.5.1) pipeline (31) on volumetric T1. Frontal region ROIs were defined as the plane passing perpendicularly the frontal lobe and tangent, on sagittal plane, to genus corpus callosum. Consequently, the fractional anisotropy (FA), apparent diffusion coefficient (ADC), axial diffusivity (AD), and radial diffusivity (RD) values were calculated. A Bayesian comparison was performed for all values between each patient's time points and the control group with *singlebayes* tool (32, 33).

Finally, a voxel-wise two-sample *t*-test was performed on FA, AD, ADC, and RD maps with SPM12 software (https://www.fil.ion.ucl.ac.uk/spm/) between each patient's time points and the control group. Briefly, maps were normalized using the high-resolution FMRIB58_template in the Montreal Neurological Institute (MNI) space applied to consider only the white matter, including only the FA values > 0.21 (34).

A threshold of $p < 0.05$ with false discovery rate (FDR) as multiple comparison correction was considered as significant.

RESULTS

Clinical and Neuropsychological Assessment

Neuropsychological evaluation evidenced a multidomain impairment. Global cognitive status was compromised, as evidenced by performance on MMSE, FAB, and MoCA. Results of CDR suggest the presence of a mild degree of dementia. The patient failed in tests for executive functions, and attention performance was borderline with respect to cutoff. Visuo-spatial abilities and fluid intelligence were preserved from deterioration. No depressive and apathetic symptoms resulted from the questionnaires. Interoceptive consciousness was inferior to normative data; finally, the patient presented several behavioral dysregulation symptoms.

Follow-up neuropsychological assessment confirmed cognitive dysfunction, but no deterioration was observed. Executive functions are the cognitive domain mainly impaired in our patient. No depressive or apathetic symptoms occurred. Interoceptive consciousness was significantly inferior with respect to normative data; behavioral alterations diminished over time with respect to first clinical evaluation. Cognitive and clinical tests are summarized in **Table 1**.

TABLE 1 | Summary of neuropsychological and clinical results at the baseline and follow-up assessments.

	T0 raw score	T2 raw score	Cut-off	Cognitive domain
MMSE	20.2	21.2	23	Global cognitive status
FAB	10	12	13.5	Executive functions screening
MoCA	19	18	26	Mild cognitive impairment
CDR	1	1	–	Dementia
Ravens' progressive colored matrices '47	26	26	18.9	Fluid intelligence
Phonological fluency	10	22	17.3	Executive functions
Semantic fluency	14.5	16.5	33.2	
Stroop test	1: 17" (t)	1: 20"		
	2: 19" (t)	2: 22"		
	3: 48" (t)	3: 50"	T:36.92	
	7 errors	7 errors	E:4.24	
Milan constructional apraxia	12	11	8	Visuo-spatial abilities
TMT	A:77	A:87	A<94	Attention
	B:249	B:132	B <283	
	B-A:172	B-A:45	B-A<186	
BDI-II	7	7	14	Depression symptoms
FBI	26	9	20	Behavioral symptoms
SAQ	22	16	27	Interoceptive consciousness
APATHY EVALUATION SCALE	33	34	38	Apathy

MMSE, Mini Mental State Examination; FAB, Frontal Assessment Battery; MoCA, Montreal Cognitive Assessment; CDR, Cognitive Dementia Rating; TMT, Trail Making Test; BDI-II, Beck Depression Inventory-II; FBI, Frontal Behavior Inventory; SAQ, Self-Awareness Questionnaire.

PET-CT

PET-CT analyses confirmed bilateral thalamic hypometabolism, more pronounced on the left side. In the left thalamus,

hypometabolism was increased between baseline and first follow-up and stationary between the two follow up (T0, $Z = -4.4$; T1, $Z = -5.6$; T2, $Z = -5.5$). In the right thalamus, there was a significant hypometabolism only in the second time point (T2, $Z = -4.3$). Moreover, in the left inferior temporal gyrus, there was hypometabolism at the baseline and second follow-up (T0, $Z = -4.1$, T2, $Z = -4.1$) but not in the first (T1, $Z = -3.3$). In the gyrus rectus, the decreased metabolism was present in the second and third acquisitions (T1, $Z = -4.3$, T2, $Z = -4.3$). Pet-ct results are presented in **Figure 1**. The other brain regions with a significant Z score are summarized in **Table 2**.

TABLE 2 | Significant metabolic brain areas resulting from PET-CT between time-points patient and database control.

	Z score		
Brain area	**T0**	**T1**	**T2**
Heschl gyrus (L)	−3.5	−3.6	−4.1
Inferior temporal gyrus (L)	−4.1	−3.3	−4.1
Middle temporal gyrus (L)	−3.8	−3.3	−4.1
Mesial temporal lobe (R)	−1.7	−2.6	−4.2
Superior frontal gyrus medial orbital (L)	−3.0	−3.0	−4.2
Superior frontal gyrus orbital part (R)	−3.7	−3.2	−4.2
Basal ganglia (L)	−3.5	−3.5	−4.3
Corpus striatum (L)	−3.5	−3.4	−4.3
Parahippocampal gyrus (L)	−1.9	−2.6	−4.3
Thalamus (R)	−3.0	−4.3	−4.3
Mesial temporal lobe (L)	−1.8	−2.5	−4.4
Gyrus rectus (L)	−3.9	−4.0	−4.5
Olfactory cortex (R)	−2.9	−3.2	−4.5
Gyrus rectus (R)	−3.7	−3.8	−4.7
Superior frontal gyrus medial orbital (R)	−3.4	−3.3	−4.7
Caudate nucleus (L)	−3.7	−3.7	−5.1
Thalamus (L)	−4.1	−5.6	−5.5

DT

Significant differences were found between patient and controls for the diffusion tractography indices. A difference on RD for the right anterior thalamic radiation in T0 ($p = 0.03$) was found when compared to the control group. The ADC (T0: $p = 0.007$; T1: $p = 0.006$) and RD (T0: $p = 0.01$; T1: $p = 0.02$) values were significantly increased in the left anterior thalamic radiation. Furthermore, at T1, an increase on ADC ($p = 0.006$) and RD ($p = 0.001$) and a decrease on FA ($p = 0.02$) were observed compared to control subjects, whereas no significant results were obtained on AD index. All tractography maps are presented in **Figure 2**.

Finally, voxel-wise analyses between normalized DT maps of control subjects and the T2 did not show significant differences.

DISCUSSION

In this longitudinal study, we evaluated three times, in about 2 years, a patient who presented with vascular dementia marked by severe bilateral thalamic lesion and that performed PET/CT and MRI. While focal unilateral thalamic infarction more frequently occurs, diffuse bilateral lesion, as the case presented in this work, is more uncommon and can determine a particular type of

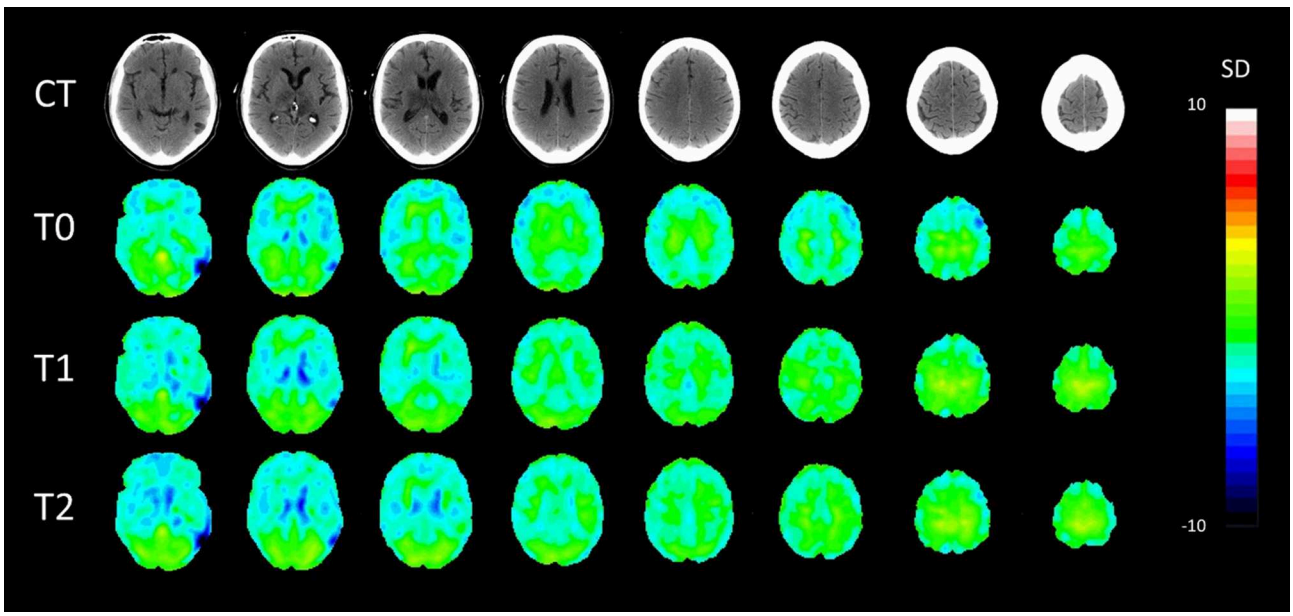

FIGURE 1 | Axial patient normalization map PET with co-registered CT in the three time points. SD, standard deviation colored scale. Slices were taken with 8 mm distance.

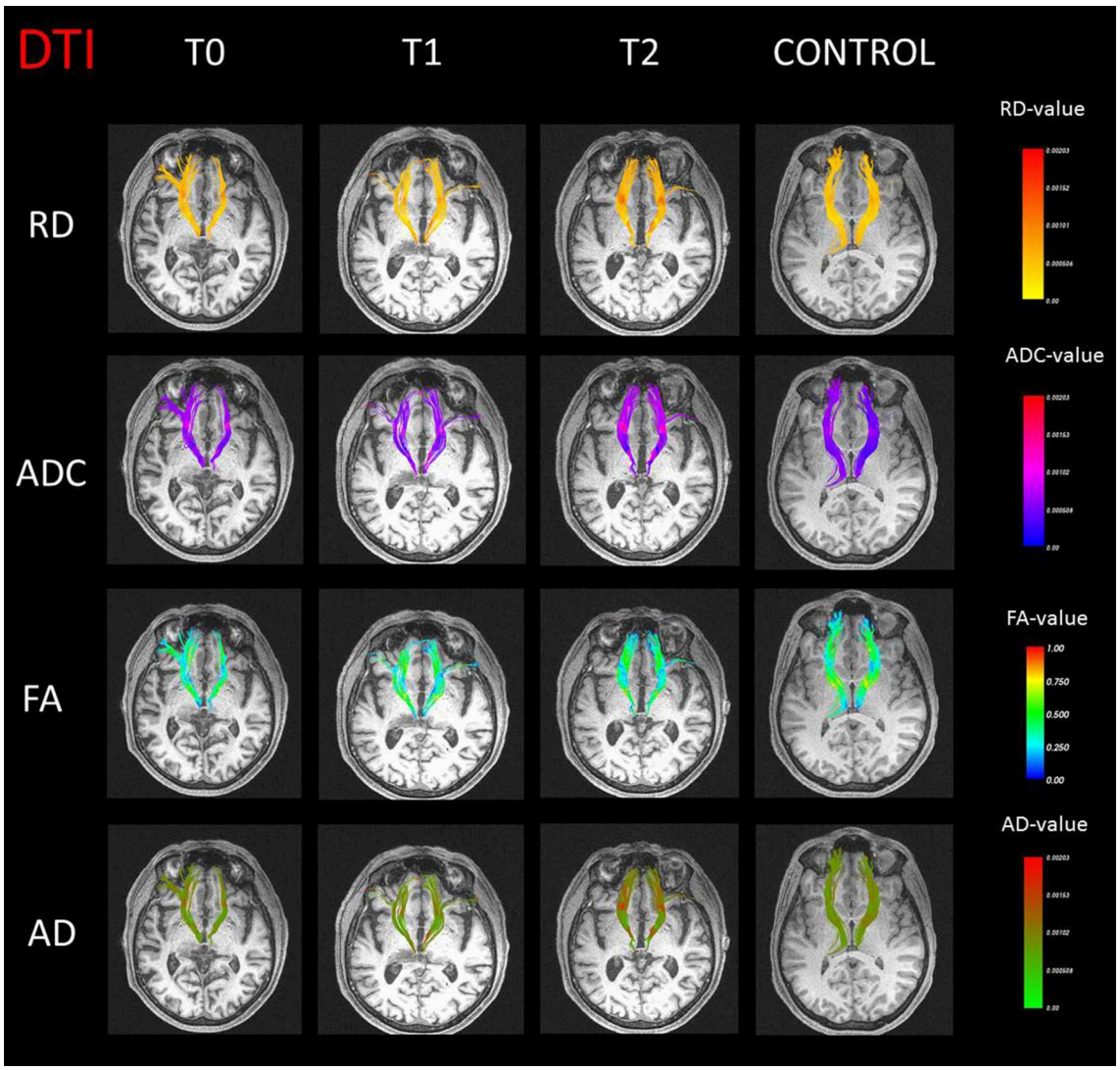

FIGURE 2 | Anterior thalamic radiation streamline representation with values of radial diffusivity (RD), apparent diffusion coefficient (ADC), fractional anisotropy (FA), and axial diffusivity (AD) in false color maps for the case (three different time points) and a representative control subject.

vascular dementia that, involving a strategic area for many neural networks (35), determines dysfunction of entire networks, not simply areas.

PET analysis highlighted a hypometabolic pattern that involved the thalami and several cortical areas; thalamic hypometabolism was quite diffuse, not permitting to identify a specific component more impaired with respect to others. Associated areas afferent primarily to temporal and frontal lobes, and representing projection areas of the thalami, showed significant reduced metabolism, as in the case of the left parahippocampal gyrus.

Since the medial dorsal and anterior nuclei of the thalamus are related to the hippocampus, they are considered to play a role in formation of new memories and project to afferent pathways from the temporal to the frontal lobe (36). This reduction might explain memory disturbances presented by the patient and resulting from the neuropsychological assessment. In this regard, the CDR revealed difficulties in detaining and recalling information regarding the recent past instead of well consolidated remote information. Such deficits we observed, attributable to an onset of dementia, are in line with von Cramon et al. (37) and Schmahmann (36) who reported that thalamus lesions can impair recent memory. Also, Serra et al. (38) observed memory impairment in two patients with bilateral thalamic lesions they studied by structural MRI; the first subject showed a mainly right damage and complained about memory deficits; the other one had a more symmetrical lesion and showed executive dysfunctions in addition to memory impairment.

Hypometabolism in the right thalamus seems to be a marker of subcortical vascular mild cognitive impairment, whereas the patients with amnestic mild cognitive impairment show

hypometabolism mainly in left parahippocampal gyrus and orbitofrontal regions (39). Moreover, the ischemic interruption of frontal subcortical circuits also affects mood and behavior and contributes to the cognitive impairment of subcortical vascular dementia (40, 41). Our patient presents a mixed condition, where the frontal lobe is involved due to the bilateral superior frontal gyrus reduced uptake compared to control subjects. The superior frontal gyrus has anatomical connections with the thalamus (42), its posterior part is generally mainly activated by motor tasks, whereas the lateral part is involved in working memory and attention and the medial part, afferent to the default-mode network, is deactivated by cognitive-related processing (43). Frontal involvement could explain behavioral symptoms presented by the patient in terms of lack of flexibility, disorganization about complex activities, perseveration, and irritability. Reduced metabolism also involved the temporal lobe, in particular temporal and Heschl gyri. Middle and inferior temporal gyri subserve language and semantic memory processing, visual perception, and multimodal sensory integration. Temporal hypometabolism is in accordance with impaired cognitive performances, especially on executive functions, in particular semantic fluency, since phonemic and semantic fluency are usually used to test neurologic damage but semantic component is more impaired following temporal lesions. Therefore, medial temporal hypometabolism found here points for a dementia diagnosis, since the patient showed a widespread impairment, revealing multidomain cognitive problems. He had altered global cognitive status and executive functions, in both the baseline and follow-up evaluation, even if the patient performed both performances slightly better on the follow-up time. The MoCA test results were in accordance with MMSE and FAB performances, confirming cognitive impairment. Among the batteries, the CDR, which is specific for characterizing level of memory decline, showed the presence of a mild level of dementia. More specifically, single tests that explore single cognitive domains showed that executive functions appeared partially altered, whereas attention, apraxia, and fluid intelligence were preserved from deterioration. On clinical tests, the patients displayed no depressive or apathetic symptoms and a normal level of interoceptive consciousness.

Levasseur et al. (44), among the first, studied seven cases of patients with bilateral thalamic infarcts by PET, showing diffuse cortical hypometabolism and associated amnesia. De Falco et al. (45) reported a patient with severe memory loss and apathy. MRI showed bilateral thalamic damage of posterior and medial areas, involving part of the pulvinar, more evident for the right thalamus. Six months later, a severe memory impairment was still evident and both MRI and SPECT findings were unchanged.

Sandson et al. (3) described the case of a patient who presented with left medial thalamic infarction evident from computerized tomography, electroencephalography, MRI, and SPECT that evidenced frontal lesions and presented with several personality changes and cognitive impairments mainly in memory, language, and executive functions domains. The authors hypothesized that the deficit of complex behavioral functions resulted from injury of the dorsomedial nucleus of the thalamus involved in the frontal network subserving these abilities.

Additionally, reduced glucose metabolism in basal ganglia, striatum, and caudate nucleus was detected. Basal ganglia are the core structures of extrapyramidal motor system, but also are involved in pathways subtending to emotional, motivational, and cognitive functions. The striatum receives inputs from cortical areas and, via the thalamus, projects to prefrontal, premotor, and supplementary motor areas. The circuit involving basal ganglia, thalamus, and cortical areas maintains movement organization, mainly involuntary and stereotyped (1). The patient complained about some difficulties in walking and pain to the right leg; therefore, we hypothesize that abnormal uptake in these areas, related to vascular outcomes he had, could explain the motor symptoms he suffers.

In line with metabolic results, analyses of tractography evidenced altered connections between the thalamus and frontal regions. All significant differences between the patient and controls involved the anterior thalamic radiation, one of the major fiber tracts in the fronto-thalamic circuitry that connects the prefrontal lobe to the anterior and dorsomedial thalamic nuclei. Reduced anisotropy and augmented diffusivity in the anterior thalamic radiation were detected in the patient, signaling a structural change of white matter (46), both in baseline and in the first follow-up evaluation. Furthermore, higher RD and ADC and reduced FA values for the anterior thalamic radiation were in line with the evidence of thalamic lesion.

Almost all imaging results presented on patients with thalamic lesions focus on brain metabolism, largely ignoring structural impairments evident with the diffusion tractography. In the present work, structural changes have been observed in the diffusion tractography index, in absence of results from voxel-wise analysis. The lack of significant differences in the latter analysis could be explained by the fact that voxel-based analysis and fiber tractography are methods using different approaches. It is plausible that results from the voxel-wise analysis were affected by an ineffective registration between subjects, since it is a fundamental prerequisite for voxel-wise group comparison. Conversely, in diffusion tractography, the tracts can be delineated without relying on subject registration. However, specific a priori regions of interest or specific tracts need to be selected for comparison, as we have done.

The most striking finding of the present work is the association between structural and metabolic changes within the fronto-thalamic circuitry in our patient. Multimodal imaging assessment longitudinally demonstrated adaptations to bilateral vascular thalamic injury at multiple levels, revealing the metabolic, functional, and microstructural alterations attending to multidomain neuropsychological impairment.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the manuscript.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRCCS Pascale Ethical Committee. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

CC interpreted the results and wrote the paper together with ML who performed neuropsychological data collection, analyses, and interpretation. MO performed MRI acquistion and tractography and PET analyses. LT performed neuroimaging acquisition and analyses of the new sample of control subjects. DG developed the study concept and design and made manuscript revision. MA and MS revised the manuscript and approved the draft.

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Alerting, Orienting, and Executive Control: The Effect of Bilingualism and Age on the Subcomponents of Attention

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Life-long experience of using two or more languages has been shown to enhance cognitive control abilities in young and elderly bilinguals in comparison to their monolingual peers. This advantage has been found to be larger in older adults in comparison to younger adults, suggesting that bilingualism provides advantages in cognitive control abilities. However, studies showing this effect have used a variety of tasks (Simon Task, Stroop task, Flanker Task), each measuring different subcomponents of attention and raising mixed results. At the same time, attention is not a unitary function but comprises of subcomponents which can be distinctively addressed within the Attention Network Test (ANT) (1, 2). The purpose of this work was to examine the neurofunctional correlates of the subcomponents of attention in healthy young and elderly bilinguals taking into account the L2 age of acquisition, language usage, and proficiency. Participants performed an fMRI version of the ANT task, and speed, accuracy, and BOLD data were collected. As expected, results show slower overall response times with increasing age. The ability to take advantage of the warning cues also decreased with age, resulting in reduced alerting and orienting abilities in older adults. fMRI results showed an increase in neurofunctional activity in the frontal and parietal areas in elderly bilinguals when compared to young bilinguals. Furthermore, higher L2 proficiency correlated negatively with activation in frontal area, and that faster RTs correlated negatively with activation in frontal and parietal areas. Such a correlation, especially with L2 proficiency was not present in young bilinguals and provides evidence for a bilingual advantage in the alerting subcomponent of attention that characterizes elderly bilinguals' performance. This study thus provides extra details about the bilingual advantage in the subcomponent of attention, in older bilinguals. Consequently, speaking more than one language impacts cognition and the brain later in life.

Keywords: bilingualism, subcomponents of attention, neuroimaging, attention network task, aging

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INTRODUCTION

Enjoying a satisfying aging, particularly with regard to cognitive health, is desirable by people globally. Not all individuals enjoy healthy cognitive functioning, and even those who do usually show structural changes in their brain with aging. The mismatch between the relative preservation of cognitive abilities in the presence of structural changes in the brain is conceived as if the brain

had some sort of "cognitive reserve," a heavily used term defined as the individual differences in cognitive task performances which provides resilience to age-related brain damage or pathology (3, 4), giving rise to disparity between the degree of brain damage or pathology and the clinical manifestation of cognitive performance. Cognitive reserve is usually estimated using different intercorrelated factors—education (5), occupation (6), and second language learning (7–9). These factors have been studied in literature over the years as proxies of cognitive reserve.

In the context of lifelong bilingualism, cognitive reserve can be conceptualized as a cognitive resilience resulting from the use of, and exposure to, two or more languages. In such a context, it is believed that practiced bilingualism provides cognitive resilience to the cognitive control mechanisms allowing to counter, partially or totally the impact of age-related changes in the brain. Various studies suggest that lifelong bilingualism, or speaking two languages on a daily basis, can result in advantage in cognitive control processes i.e., how individual with high or low level of bilingualism or when compared to their monolingual peers differ in their behavioral (7, 10–12) and brain functions (11, 13–17). For example, it has been reported that elderly bilinguals show faster response time and make fewer errors than their monolingual peers on attentional control tasks (7, 18). Over the years, neuroimaging studies have also shown neural efficiency for bilingual elderly groups when compared to monolingual counterparts suggesting less activity in the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) (11, 13, 16). Interestingly, 13 showed a comparable neurofunctional activation pattern for elderly bilinguals when compared to young adults. However, they outperformed monolinguals peers while showing less activation in frontal regions in a task-switching paradigm. Thus, suggesting neuroprotective effects of bilingualism in older adults on cognitive control processes. Furthermore, such a bilingual advantage in older adults is seen as a different strategy in cognitive control mechanism i.e., in the proactive mode of cognitive control (16). In proactive mode of cognitive control, attention is recruited as an "early selection" mechanism that relies on anticipation and prevention of interference before it occurs (19). In addition, functional connectivity studies have also supported better neural efficiency in bilinguals by demonstrating stronger resting state functional connectivity between anterior to posterior brain areas (14) and default mode network (DMN), and fronto-parietal cortex (17) for bilinguals compared to monolingual older adults. Berroir et al. (15) also suggest efficient performance for the bilingual older adults in the task-based functional connectivity measures.

At the same time, cognitive control is not a single mechanism (selection, inhibition, interference, switching, etc.) and it is thought to operate via the attentional functions (19) in a goal-directed manner. In fact, attention consists of subcomponent processes that are separable, yet interconnected which determines the order of the information processing (2, 20). These subcomponents of attention—alerting, orienting and executive control—can be measured by using the Attention Network Test (ANT, 1) whose validity has been proven across a variety of populations (21, 22). The neurofunctional bases of the three subcomponents of attention are themselves different from each other (1). Alerting function has been associated with various frontal and parietal regions with strong thalamic involvement. Orienting network has been associated with parietal sites and frontal eye field. Anterior cingulate cortex (ACC) as well as dorsolateral prefrontal cortex (DLPFC) are associated with execution network (1, 22). Very few studies have looked at the role of bilingualism on the subcomponents of attention (12, 23, 24). Moreover, these studies essentially focused on a behavioral comparison with monolingual individuals, suggesting enhanced alerting (12) and executive control (12, 23, 24) with no difference in orienting ability in bilinguals. And none of these studies compared the performance within bilingual groups varying in L2 age of acquisition (early vs. late), usage (balanced vs. unbalanced) or proficiency (high vs. low). There are studies that support the role of bilingualism on cognitive performance by performing correlation analysis of the measures of bilingualism (L2 usage and proficiency, age of acquisition) (25) with cognitive task (26, 27) instead of comparing dichotomous groups (like monolingual vs. bilingual; High proficient vs. low proficient bilinguals). In a study by Tse and Altarriba (26), more proficient individuals were better at maintaining attention during the task and these results were supporting the bilingual advantage. In addition, Luk et al. (27) also reported a positive correlation between age of onset of active bilingualism and flanker effect, suggesting that early bilingual experience resulted in greater advantage in cognitive control performance. Given that bilingual experience is dynamic in nature, the idea of treating bilingualism as a continuous variable is important (25, 28, 29).

In addition, age-related changes in elderly population—without measures of bilingualism—show significant reduction in the alerting (30, 31) and executive control abilities (31) when compared to young adults. However, the behavioral and neurofunctional bases of bilingual advantages in subcomponents of attention in aging remain unknown. In the present study, it is proposed to use the functional magnetic resonance imaging (fMRI) and the attention network task to understand the role of bilingualism while controlling for education—other proxies of cognitive reserve—to better understand the dynamic nature of interaction in aging population. The bilingual advantage conferred by lifelong use of two languages in aging may be associated with improved behavioral and neural efficiency. The goal of this study is thus to determine whether elderly bilinguals' show a behavioral and neurofunctional advantage over young adults—matched on measures of bilingualism as well as education—in different subcomponents of attention as measured by the ANT task. It is expected that older bilinguals will show longer response time and lesser accuracy, in the ANT performance. This will be reflected by an increase in the executive control effect and decrease in alerting and orienting effects in older bilinguals. In terms of fMRI data, we expect more neurofunctional activation in the older bilinguals when compared to young bilinguals in the executive control and alerting abilities (30, 31). More specifically, we expect that older bilinguals will recruit more fronto-parietal areas and anterior cingulate cortex when compared to young bilinguals for the ANT task performance. For the bilingual advantage hypothesis, we

TABLE 1 | Demographic, neuropsychological, and language measures of both the groups.

	Young adult ($N = 20$)	Older adult ($N = 18$)	*t*	Sig. (2-tailed)
	Mean (SE)	Mean (SE)		
Demographic information				
Age	32.6 (0.7)	73.9 (0.6)	−41.6	0.00*
Education	18.7 (0.7)	16.8 (0.6)	1.8	0.087
Gender	Female = 9	Female = 11		
Neuropsychological assessments				
MoCA	29.2 (0.1)	28.61 (0.2)	1.9	0.095
TMT A	16.8 (0.7)	30.09 (1.9)	−6.4	0.00*
TMT B	39.7 (2.3)	60.02 (5.3)	−3.5	0.00*
OBT_RT	751.3 (34.1)	931.5 (40.7)	−3.4	0.00*
OBT_Acc	0.9 (0.007)	0.8 (0.01)	1.7	0.098
Subjective measures of LP				
L2: Percent exposure	26.5 (3.4)	18.3 (2.8)	1.7	0.08
L2: AoA-Speaking	7.4 (0.7)	8.3 (0.7)	−0.9	0.36
L2: AoA-Reading	10.7 (0.9)	12.9 (1.1)	−1.4	0.15
L2: LP-Speaking (Max:10)	7.3 (0.3)	6.2 (0.4)	1.8	0.07
L2: LP-Reading (Max:10)	7.9 (0.3)	7.2 (0.3)	1.6	0.12
Objective scores on the measures of LP				
L2 LexTale (%)	80.5 (2.3)	81.9 (2.1)	−0.4	0.66
L2 BNT (Max:60)	48.8 (1.4)	46.2 (1.3)	1.3	0.19
L2 RC (Max:11)	5.9 (0.4)	6.2 (0.43)	−0.5	0.60
L2 Discourse (Max:18)	17.02 (0.1)	16.7 (0.3)	0.7	0.43
L2 Composite LP scores (%)	77.5 (0.01)	77.2 (0.01)	0.1	0.89

*SE, Standard error; MoCA, Montreal Cognitive Assessment; TMT, Trial Making Test; OBT, One back Test; RT, Response time; Acc, Accuracy; LP, Language Proficiency; L2, Second Language; AoA, Age of Acquisition; BNT, Boston Naming Test; RC, Reading Comprehension; *, significant.*

expect the negative correlations between L2 measures (age, usage, and proficiency), and ANT behavioral performance and BOLD activation for the subcomponents of attention.

METHODS

Participants

Thirty-eight French-English bilingual young adults (YA; mean age 32.6 ± 3.1 years; $N = 20$; 9 females) and old adults (OA; mean age 73.94 ± 2.8 years; $N = 18$; 11 females) with no history of neurological or psychiatric disease were included in the study. A signed informed consent approved by the CRIUGM was obtained from each participant before the experiment.

Tasks

Neuropsychological Assessment

All participants completed a detailed standardized neuropsychological assessment, which covered multiple cognitive domains. General cognitive function was assessed by the Montreal Cognitive Assessment test (MoCA) (32). Attention was assessed by the Trail Making Test (TMT A and B) (33). One Back Test (OBT) (34) and digit span task (from MoCA) were used to identify the working memory performance. Geriatric Depression Scale (GDS scale) (35) was used to rule out older participants who are suffering from depression. Further, both the groups were from similar socioeconomic background and were matched on education level. In addition, performance on general cognitive assessment (MoCA) was equivalent across groups, indicating similar cognitive ability (Refer to **Table 1**).

Measures of Bilingualism

Second language (L2) age of acquisition (AoA), language usage and proficiency were established by the Language Experience and Proficiency Questionnaire (LEAP-Q) (36), a widely used subjective measures of bilingualism (Refer to **Table 1**). LEAP-Q was used to collect information on the L2 speaking and reading AoA, percentage of L2 usage in daily life in speaking and reading domains, as well as self-reported L2 speaking and reading proficiency (Refer to **Table 1**). Four objective measures of L2 proficiency were also included (a) L2 proficiency in confrontation naming (Boston Naming Test) (37), (b) L2 proficiency in discourse production[1] using pictures from Western Aphasia Battery (41) and Boston Diagnostic Aphasia Examination (42) that provides a composite rubric score (38, 39), (c) L2 proficiency in reading comprehension using a part of York adult assessment battery- revised [YAA-R; (43)], and (d) L2 proficiency in vocabulary skills using LexTale test (44).

Attention Network Test (ANT)

We used event-related fMRI to study the activations of the different subcomponents of attention. This task is a combination of the cueing paradigm (45) and the flanker task (46). Participants were presented with five white arrows on a black background and were asked to determine the direction of the target arrow in the middle—left or right. The arrows were presented either above or below a centrally located fixation cross. The target arrow was flanked by pairs of congruent arrows or incongruent arrows, resulting in two flanker conditions—congruent and incongruent, respectively. Furthermore, three types of warning cues were used: no-cue (baseline), alert cue (temporally informative), and spatial-cue (temporally and spatially informative). The efficiency of the three attentional effects was assessed by measuring how response times are influenced by different warning cues and flanker conditions resulting in alerting (No cue vs. alert cue), orienting (Spatial cue vs. alert cue) and executive control (Incongruent vs. congruent flanker condition) effects. Each trial begins with a fixation window, followed by the cue window lasting for 300 ms. After a variable duration (one of a set of 12 discrete times from 300 to 6,300 ms, approximating an exponential distribution with a mean interval of 2,100 ms), the stimuli appear either above or below the fixation point (based on the warning cue) within two degrees of visual angle until the participant responded or 2,000 ms elapsed. The duration between the onset of the target

[1]L2 discourse scores consist of a composite rubric score (Maximum = 18) that is performed with the help of scoring sheet (38–40), in which total score is calculated by summing the scores on the following aspects: Overall impact and achievement of purpose, Organization and technique, and Mechanics (38–40). Two independent high proficient rates listen to the audio recording and rate the performance on this rubric. Average of the two raters' response is taken as the final score for the L2 proficiency in discourse production.

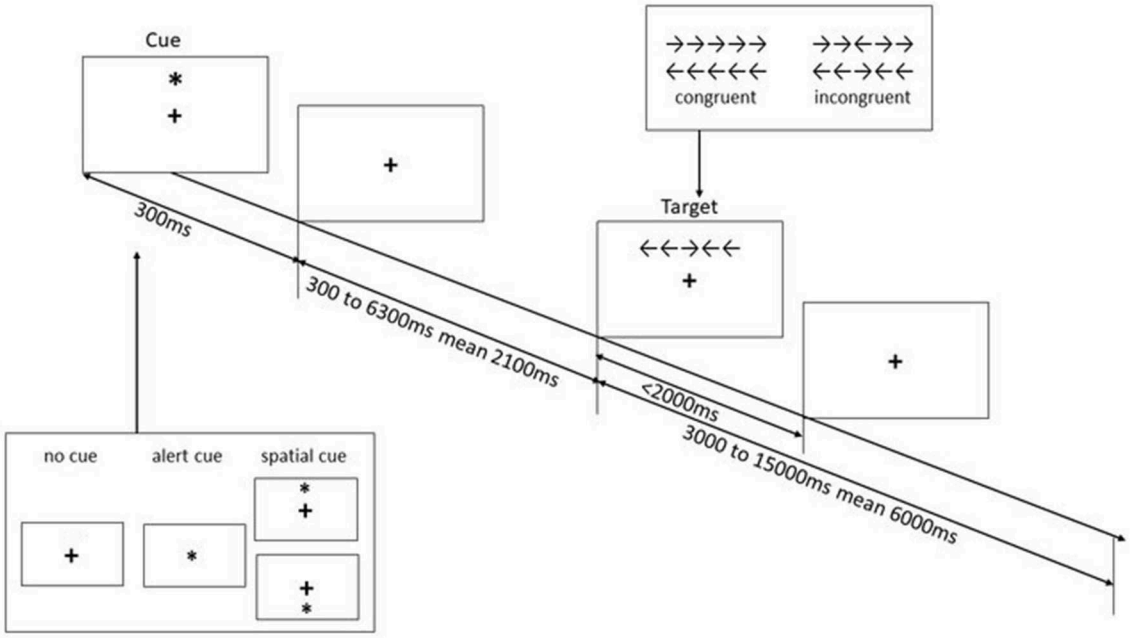

FIGURE 1 | Schematic of attention network test (1). This figure illustrates the time course of the warning cues and the flanker condition.

and the start of the next trial was also jittered (a set of 12 discrete times from 3,000 to 15,000 ms, approximating an exponential distribution with a mean of 6,000 ms; refer to **Figure 1**). A total of 144 trials (72 for each flanker conditions, namely congruent and incongruent) with different warning cues were recorded in three runs. Each run consists of a 2-buffer trial at the beginning of the run, which was not included in the analysis.

Image Acquisition and Processing

MR imaging was carried out using 3T MRI Siemens Prisma Fit scanner with a standard 64-channel head coil. The image sequence was a T2 weighted pulse sequence (TR = 785 ms; TE = 30 ms; matrix = 64 × 64 voxels; FOV= 192 mm; flip angle = 54°; slice thickness = 3 mm; and acquisition = 39 slices). A high-resolution structural image was obtained before the three functional runs using a 3D T1-weighted imaging using an MPRAGE sequence (TR = 2,400 ms; TE = 2.33 ms; 240 slices; matrix = 256 × 256 mm; voxel size = 0.8 × 0.8 × 0.8 mm; and FOV= 230 mm). Imaging data were pre-processed and analyzed using SPM12 (Wellcome Department of Imaging Neuroscience, UK) running with MATLAB (Mathworks, USA). To correct for between-scan movements, the functional images were realigned to the first image of each session. Each participants' structural T1 image was then co-registered to the mean functional image. The functional images were then spatially normalized into the standard space defined by the Montreal Neurological Institute (MNI) template. After normalization, all scans were resampled at a resolution of 2 × 2 × 2 mm. The functional images were spatially smoothed with an isotropic Gaussian kernel (full width at half maximum of 8 mm) to increase the signal-to-noise ratio.

Statistical Analysis

Behavioral Data Analysis

Raw response time, accuracy rate and inverse transformed response time (RTinv = −1,000/RT) were used for the data analysis. Inverse transformation was performed to normalize the positively skewed response time distribution. Mixed ANOVA and ANCOVA were performed with groups (OA vs. YA) as between-subject variable and flanker conditions (congruent vs. incongruent) and warning cues (no, alert, or spatial) as the within-subject variables for the accuracy and RTinv data (with average response time of each participant as covariate), respectively. The overall slowing of stimulus perception and motor response for the older adults have confounding effect of age (47) in the behavioral measures of ANT performance. To address this concern in the response time analyses, ANCOVAs using average response time as a covariate was conducted. Also, incorrect responses and the trials with response time exceeding three standard deviations were excluded from the analysis. Ratio scores were subsequently computed for the alerting effect [(No cue–Alert cue)/Alert cue], orienting [(Alert cue–Spatial cue)/Spatial cue] and the executive control effect [(Incongruent–Congruent)/Congruent] using the raw response time. Furthermore, these scores were introduced for a planned comparison between the groups using independent sample *t*-test. Instead of the conventional subtraction measure (1, 12), ratio scores were used to define the efficiency of the subcomponents of attention, thus, reducing the influence of the overall response time (RT) on the alerting, orienting and executive control effects (48, 49).

TABLE 2 | Mean RT (and SD) and accuracy (and SD) for each condition during ANT behavioral performance.

Flanker condition	Age group	Warning type		
		No cue	Alert cue	Spatial cue
Accuracy				
Congruent	YA	97.5 (0.7)	98.5 (0.7)	98.2 (0.7)
	OA	97.6 (1.1)	97.6 (0.8)	98.5 (0.8)
Incongruent	YA	91.4 (1.8)	91.6 (1.6)	95.2 (1.2)
	OA	93.2 (2.5)	94.2 (1.9)	96 (1.2)
Response time				
Congruent	YA	631.11 (74.9)	604.23 (71.3)	536.45 (60.9)
	OA	846.37 (161.2)	821.75 (157.5)	787.12 (139.0)
Incongruent	YA	698.38 (82.2)	678.56 (85.83)	601.77 (91.6)
	OA	887.35 (145.01)	887.42 (152.6)	828.79 (159.74)

YA, Young Adults; OA, Older Adults.

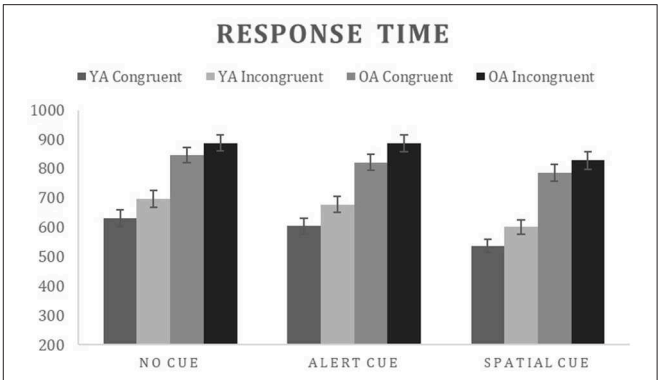

FIGURE 2 | Mean response time and accuracy for each condition on the attention network task. OA, Older adults; YA, Young adults.

fMRI Data Analysis

The general linear model (GLM) in SPM was used to conduct a whole-brain analysis of the fMRI data. We created a design matrix using the onset time of the events (separate events for no, alert, spatial cues, and congruent and incongruent flanker conditions with correct responses only). Incorrect responses and the buffer trials of each run were combined as an extra column in the design matrix. These events were convolved with the canonical hemodynamic response function (HRF), and the six motion correction parameters for each functional run were included in the design matrix as covariates of no interest. The regressors were fitted to the fMRI data to produce beta estimates for each regressor. Individual subject and second level (random effects) group analyses were conducted. Contrasts were same as the behavioral analysis, except inverted for the alerting and orienting effects (i.e., alerting fMRI effect = alert cue beta estimate – no cue; orient fMRI effect = Spatial cue beta estimate – alert cue). Only effects surviving an uncorrected voxel-level threshold of $P < 0.001$ and/or a cluster level familywise error (FWE) corrected threshold of $P < 0.05$ were interpreted with cluster size of at least 20 voxels. For group-level analyses, the independent sample *t*-test was performed to assess the difference between the young and older adults for each contrast—alerting, orienting and executive control contrast (i.e., executive control fMRI effect = incongruent beta estimate – congruent condition). In absence of any group difference, the one-sample *t*-test was performed to determine group-level activation for that particular contrast. Region-of-interest (ROI) analyses were performed for each of the three contrasts based on the previous study (1), with a priori defined ROIs of 5 mm radius. The percent signal changes within the pre-determined ROIs (1) were calculated using MarsBar toolbox (50) for each of the contrast and were analyzed using the independent sample *t*-test between the groups using SPSS.

Correlation Analysis

The relationship between measures of bilingualism (subjective and objective measures of L2 performances) and attention performance (behavioral and neurofunctional) was further examined by doing a Pearson correlation analysis with adjusted *p*-values controlling for multiple comparisons. Also, behavioral and neurofunctional performance were correlated to assess the relationship between activation pattern and the behavioral measures of ANT performance. To do so, composite factor scores for the measures of bilingualism and behavioral performance (Accuracy and response time) was calculated by performing a principal component analysis with varimax rotation method. This allows to reduce the number of correlations and avoids the effect of cross-correlations between different factor scores. In the factor analysis, factor scores were calculated using the Bartlett method in SPSS, which were then used in the correlation analysis.

RESULTS

Behavioral Results

Accuracy for the correct trials was submitted to a mixed ANOVA with group as a between subject variable (YA and OA) and warning cue (no, alert, spatial) and flanker condition (congruent, incongruent) as within subject variables. The main effects of warning cue [$F_{(2, 72)} = 41.06$, $\eta_p^2 = 0.533$, $p < 0.000$], and flanker condition [$F_{(1, 36)} = 54.54$, $\eta_p^2 = 0.602$, $p < 0.000$] were significant. The only significant interaction was between warning cue and flanker condition [$F_{(2, 72)} = 36.57$, $\eta_p^2 = 0.504$, $p < 0.000$] indicating that the flanker effect (Incongruent > congruent) was present only for the no cue and spatial warning cues (**Table 2** for details). RTinv for correct trials were submitted to a 2*3*2 ANCOVA with group as a between subject variable (OA and YA) and warning cue (no, alert, spatial) and flanker condition (congruent, incongruent) as within-subject factors, with average response time of each participant as covariate (**Figure 2**). Response times varied as a function of warning cue [$F_{(2, 70)} = 9.82$, $\eta_p^2 = 0.219$, $p < 0.000$; no cue > alert cue > spatial cue] and flanker condition [$F_{(1, 35)} = 5.204$, $\eta_p^2 = 0.129$, $p = 0.029$; Incongruent > congruent], with significant two way interaction between warning cue and flanker condition [$F_{(2, 70)} = 3.58$, $\eta_p^2 = 0.093$, $p = 0.033$] indicating that the flanker effect (Incongruent > congruent) was present for all warning cues,

TABLE 3 | Results from the random-effects analyses for the alerting, orienting, and executive control condition, for young and older adults.

Contrast	Anatomical region	WB/ROI	Area	Side	MNI coordinates			Volume
					x	y	z	
Alerting								
OA∩YA"	Fusiform gyrus	WB	BA 37	Rt	42	−56	−14	899
		WB	BA 37	Lt	−40	−62	−6	703
	Precentral gyrus	WB	BA 6	Lt	−46	2	34	82
		WB	BA 6	Rt	46	4	40	138
OA > YA*	VLPFC	WB	BA 10	Lt	−26	50	−10	24
	IFG	ROI	BA 47	Lt	−33	31	−3	
Orienting								
OA∩YA"	Visual association area	WB	BA 18	Lt	−10	−98	4	413
		WB	BA 18	Rt	10	−96	8	153
		WB	BA 18	Lt	−20	−78	−10	115
		WB	BA 18	Rt	18	−76	−14	139
OA>YA*	Superior parietal gyrus	WB	BA 39	Rt	42	−50	28	29
Executive control^								
Young adults		WB	BA 19	Lt	−4	−86	36	28
Older adults	Isthmus of CG	WB	BA 30	Lt	−22	−50	6	20

*Reverse contrast showed no effect.

^Conjunction and disjunction analysis did not result in any effect.

"Survived cluster level FEW. k > 20. IFG, Inferior frontal gyrus; VLPFC, ventrolateral prefrontal cortex; CG, Cingulate gyrus; WB, Whole Brain; ROI, Region of Interest.

however, alerting effect (No cue > Alert cue) for the incongruent condition was not significant, indicating difficulty in processing the alerting cue for the participants in conflict trials. A significant main effect of group [$F_{(1, 35)} = 5.887$, $\eta_p^2 = 0.144$, $p = 0.021$] as well as interaction between group and flanker condition [$F_{(1, 35)} = 6.27$, $\eta_p^2 = 0.152$, $p = 0.017$] and a group and warning [$F_{(2, 70)} = 7.13$, $\eta_p^2 = 0.169$, $p = 0.002$] were observed. The nature of the interaction between age and warning cue is readily apparent in **Figure 2**. For Older adults, the magnitude of warning cue effects—alerting (No cue – Alert cue) and orienting effect (Alert cue – Spatial cue)—were smaller when compared to young adults, indicating that with increasing age the ability to take advantage of the warning cues reduces. As for the interaction effect between group and flanker condition, young adults showed the desired flanker effect (Incongruent > Congruent) for all the warning cues, whereas older adults showed flanker effect only for the alerting cue. Thus, resulting in smaller interferences effect for the older adults when compared to young adults.

A significant three-way interaction for group, flanker condition and warning cue [$F_{(2, 70)} = 5.29$, $\eta_p^2 = 0.131$, $p = 0.007$] showed a larger alerting, orienting and executive control effect for the young adults. The effect of the covariate—verage response time—was significant indicating that some of the age-related difference in response time observed for the warning cue and flanker conditions can be attributed to general slowing [$F_{(2, 70)} = 3.63$, $\eta_p^2 = 0.094$, $p = 0.032$]. However, the effect of group remained significant after controlling for age-related slowing, suggesting that age-related changes in attentional ability other than general slowing also contributed to differences in response time between younger and older adults. *Post hoc* analysis of the three-way interaction showed significant group differences for the congruent condition for all warning cues ($p < 0.05$) indicating older adults are slower than younger adults on taking advantage from the warning cues on trials without any conflict (i.e., congruent). For the incongruent condition, group difference was evident only for the spatial cue (OA > YA; $p < 0.05$) indicating that in the conflict condition (i.e., incongruent), older adults were slower to take advantage from the temporally and spatially informative cue (i.e., spatial cue). And the planned comparison of the ratio scores for the three subcomponent of attention revealed that older adults (relative to young adults) showed a numerically smaller alerting [$t_{(36)} = 2.13$, $p = 0.03$], orienting effect [$t_{(36)} = 3.58$, $p = 0.001$] as well as significantly smaller interference effect [i.e., executive control effect; $t_{(36)} = 2.68$, $p = 0.01$].

fMRI Results

Firstly, we identified common brain regions that were consistently engaged in young and older adults for each subcomponent of attention in a random effect analyses (see **Table 3**). Secondly, two-sample *t*-test was performed on contrast images to assess the significance of any group differences observed in the activation patterns between young and older adults for different subcomponents of attention (see **Table 3**; **Figures 3–5**).

Comparison Between Young and Older Adults for the Alerting Effect

The conjunction analysis[2] on the brain activity associated with the alerting (Older adults n Young adults), defined as increased activity in alert cue trials vs. no cue trials, showed activation in the bilateral fusiform gyrus (BA 37) and pre-Supplementary Motor

[2]Conjunction analyses involves identifying brain areas that show significant activation across the experimental condition, in the present study across the group (YAnOA). In contrast, disjunction analyses identify significant activation that is present in one experimental condition and not the other (OA > YA or reverse).

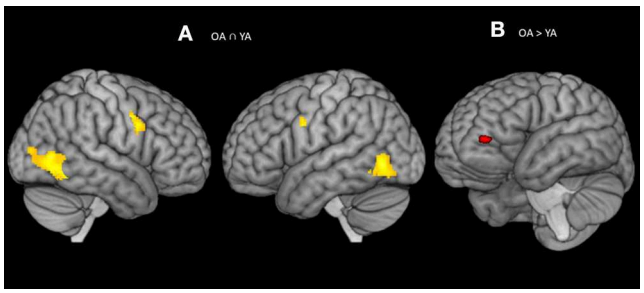

FIGURE 3 | (A) Significant blood-oxygen-level dependent (BOLD) signal increase related to the alerting contrast (Alert cue – No cue) in both the groups together (OA n YA) revealed bilateral activation in the fusiform gyrus (BA 37) and pre-SMA (BA 6). **(B)** Significant blood-oxygen-level dependent (BOLD) signal increase related to the alerting contrast in the Older bilinguals in comparison to young bilinguals (OA > YA) revealed activation in the ventrolateral PFC (BA 10). Statistical parametric maps overlaid on the average T1-weighted anatomy of all subjects ($p < 0.001$ and $K > 20$).

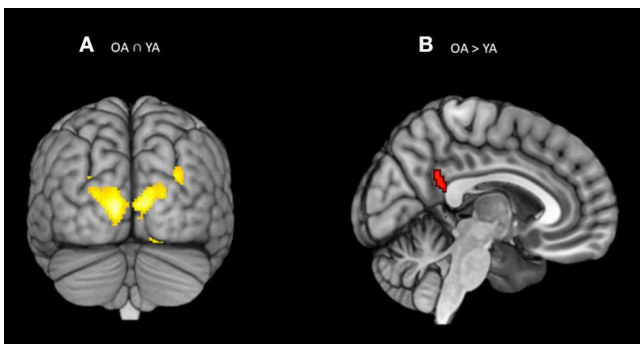

FIGURE 4 | (A) Significant blood-oxygen-level dependent (BOLD) signal increase related to the orienting contrast (Spatial cue – alert cue) in both the groups together (OA n YA) revealed bilateral activation in the visual association areas (BA 18). **(B)** Significant blood-oxygen-level dependent (BOLD) signal increase related to the orienting contrast in the Older bilinguals in comparison to young bilinguals (OA > YA) revealed activation in the superior parietal gyrus (BA 39). Statistical parametric maps overlaid on the average T1-weighted anatomy of all subjects ($p < 0.001$ and $K > 20$).

Area (pre-SMA; BA 6) (see **Table 3**; **Figure 3A**). The no and Alert cues trials were collapsed over congruent and incongruent flanker conditions. Disjunction analysis (Older adults > young adults) revealed differential increases in neural activity in the left ventrolateral prefrontal cortex for the older adults (Lt BA 10, $p = 0.001$ uncorrected, $k > 20$) (**Figure 3B**; **Table 3**). No significant activation was observed for the reversed contrast. Neural correlates of alerting were also observed in the pre-defined regions-of-interest within the left inferior frontal gyrus [Lt BA 47, defined in Fan et al. (1)]. We did not find any group difference for the rest of the pre-defined ROIs.

Comparison Between Young and Older Adults for the Orienting Effect

The conjunction analysis on the brain activity associated with the orienting ability (Older adults n Young adults), defined as increased activity in spatial cue trials vs. alert cue trials, showed activation in the bilateral visual association areas (BA 18; see **Table 3**; **Figure 4A**). The two-sample *t*-test (Older adults > young adults) revealed differential increases in neural activity in the right superior parietal gyrus close to temporal parietal junction (Rt BA 39, $p = 0.001$ uncorrected, $k > 20$) (**Figure 4B**; **Table 3**). The reverse contrast revealed no significant increases in neural activations for young adults relative to older adults. Same as alerting ability, the Spatial and Alert cues were collapsed over congruent and incongruent flanker conditions. No significant activation was found within the a priori defined regions-of-interest for the orienting contrast.

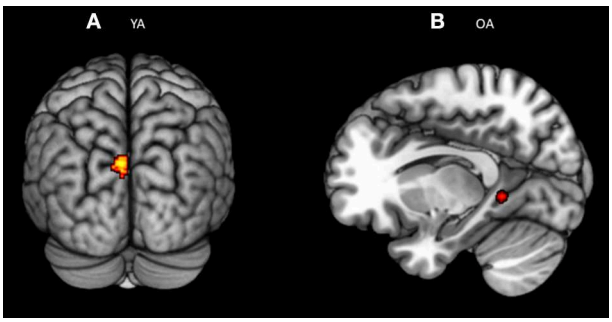

FIGURE 5 | Significant blood-oxygen-level dependent (BOLD) signal for **(A)** young bilinguals and **(B)** older bilinguals for the executive control contrast (Incongruent – Congruent). Statistical parametric maps overlaid on the average T1-weighted anatomy of all subjects ($p < 0.001$ and $K > 20$).

Comparison Between Young and Older Adults for the Executive Control Effect

Whole brain analysis as well as Region-of-interest analysis did not show any significant neural activation common to both the groups (Older adults n young adults) or distinct between groups (Older adults > < young adults) for the executive control effect, defined as an increase in brain activity in incongruent vs. congruent conditions, by collapsing all the warning cues together. However, we identified brain regions that were consistently engaged in young bilinguals and in older bilinguals, in separate random effects analyses for executive control effect (Incongruent > congruent). Older adults showed activity in the isthmus of left cingulate gyrus [Left BA 30; $p = 0.001$ (uncorrected), $k > 20$] whereas young adults recruited more posterior brain for the same task [Left middle occipital gyrus BA 19 $p = 0.001$ (uncorrected), $k > 20$; **Figure 5**].

Relationship Between Neurofunctional Activation and Behavioral Measures

Results from the individual factor analysis of the subjective and objective measures of bilingualism (Refer to **Table 1**) produced a single and two-factor solution, respectively (refer to **Tables 4A,B** for details). All the subjective measures of bilingualism—LEAP Q—yielded a single factor structure. The factor analysis (**Tables 4A,B**) of the objective measures resulted in two-factors: L2 proficiency in discourse production and rest of the objective

TABLE 4A | Combined factor analysis of both the groups for the ANT behavioral performance.

			ANT behavioral performance					
	Factor	**Variance**	**No congruent**	**Alert congruent**	**Spatial congruent**	**No incongruent**	**Alert incongruent**	**Spatial incongruent**
Factor 1	Response time	49.06%	0.971	0.973	0.969	0.971	0.968	0.964
Factor 2	Accuracy for incongruent conditions	20.15%				0.822	0.846	0.761
Factor 3	Accuracy for congruent conditions	10.90%	0.825	0.595	0.463			

TABLE 4B | Combined factor analysis of both the groups for the measure of bilingualism.

			Objective measures of bilingualism				Subjective measures of bilingualism						
	Factor	**Variance**	**L2 naming**	**L2 vocabulary**	**L2 reading Comprehension**	**L2 discourse production**	**Factor**	**Variance**	**L2 language exposure**	**L2 AoA speaking**	**L2 AoA reading**	**L2 speaking proficiency**	**L2 reading proficiency**
Factor 1	L2 naming, vocabulary and reading comprehension	45.85%	0.919	0.767	0.656	0.95	Single factor	52.87%	0.710	−0.481	−0.660	0.835	0.881
Factor 2	L2 discourse production	27.25%				0.917							

measures (L2 naming, L2 reading comprehension, and L2 vocabulary). Similarly, ANT behavioral performance resulted in three-factor solution—response time measures, accuracy measure for incongruent flanker condition and accuracy for congruent flanker condition.

Pearson's correlation analyses were conducted to examine the links between behavioral effects—using the factor scores—and brain activation in the corresponding subcomponent of attention. To test for the relationship between the attentional abilities to more general neuropsychological performance as well as with proxies of cognitive reserve—education and measures of bilingualism—we correlated activation thresholds with the neuropsychological measures, education, and measures of bilingualism. Also performed partial correlations with education as covariate to find the relationship with the measures of bilingualism. We then apply Bonferroni correction for multiple testing to the results. We find a positive correlation between the neural activity of the VLPFC (BA 10) and the composite factor score for the response time (all the flanker conditions and the warning cues ($r = 0.455$; $p = 0.001$), indicating that with an increase in neural activity there is an increase in behavioral response time. There was no significant correlation between the neural activity of the superior parietal region (BA 39) related to orienting ability and the factor scores for accuracy and response time measures However, we find a positive correlation between the response time on the working memory task and the BA 39 activity ($r = 0.454$, $p = 0.004$), indicating increased neural activity of BA 39 with an increase in response time. Factor scores of behavioral ANT performance—i.e., Factor 1 = representing a composite measure of accuracy on congruent condition—showed a positive correlation with the factor scores of L2 proficiency in discourse production across the group ($r = 0.624$, $p = 0.01$) while controlling for education as a covariate. Interestingly, this correlation was significant with the older bilinguals only (OA, $r = 0.607$, $p = 0.01$; YA, $r = 0.34$; $p = 0.23$). Factor scores of behavioral ANT performance (Factor 3 representing composite measure of accuracy on congruent condition) showed positive correlation with the factor scores with Factor 2 of the objective measure of bilingualism (L2 proficiency in discourse production; $r = 0.624$, $p = 0.01$) and more so for older bilinguals ($r = 0.607$, $p = 0.01$), while controlling for education as covariate. BOLD activity for the VLPFC (BA 10)—indicating an increase in neural activity for the alerting ability in elderly—showed negative correlation with Factor 2 of the objective measure of bilingualism (L2 proficiency in discourse production; $r = -0.517$, $p = 0.001$) across group; with the older bilinguals there was an increase in this correlation value ($r = -0.655$) indicating that with an increase in L2 proficiency in discourse production there is a decrease in BOLD activity for the region related to alerting ability. For the alerting contrast (OA > YA) no significant correlation was seen with education level. Also, partial correlation continues to give similar results while controlling for education (covariate), BOLD activity of VLPFC continue to show a negative correlation with L2 proficiency in discourse production ($r = -0.523$, $p = 0.001$). For the orienting contrast (OA > YA), no correlation was seen between the BOLD activity and the proxies of cognitive reserve—education and bilingualism (with and without partial correlation).

DISCUSSION

The study intended to describe the fMRI brain activation patterns associated with the subcomponents of attention in young and elderly bilinguals, and to look for the association with the measures of bilingualism—L2 age, usage, and proficiency.

Two groups of participants i.e., young and elderly bilinguals performed the Attention Network task during fMRI scanning. L2 usage and proficiency were looked at as influencing the pattern of activation for the subcomponents of attention in young and old bilinguals. Both the groups—young and elderly bilinguals—were matched on the factors of education level, and L2 usage and proficiency, as well as for neuropsychological variables and L2 usage and proficiency were normally distributed within each group, thus making them continuous variables. Response times (RTinv), accuracy rates, and BOLD activation on flanker conditions—congruent and incongruent—and warning cues—no, alert and spatial cues—were computed, to examine alerting, orienting, and executive control effects in young and older bilinguals. As a whole, neurofunctional and behavioral results show that alerting and orienting abilities are significantly lower in elderly bilinguals as compared to young bilinguals, a finding that is associated with an increase in neural activity in elderly bilinguals, particularly in the fronto-parietal complex, sub-serving top-down attention control processes.

More specifically, both age groups were equivalent in terms of accuracy of responses. Conversely, significant differences in response times across groups show that the elderly bilinguals do not benefit from warning cues as much as the young do, and get more distracted by flankers, particularly when there is a spatial cue. These findings replicate previous findings with the ANT, showing larger executive control effects and smaller alerting effects, in older adults as compared to younger adults (30, 51–53). Also, in line with the results of previous behavioral studies showing age-related decline specific to the executive control ability only (31). Previous studies with bilingual population converge with the notion that a bilingual advantage is seen in executive control when compared to monolingual groups (12, 23, 24, 54). In the present study, the age-related differences were not evident in the incongruent condition as the experimental groups were balanced for L2 age of acquisition, language usage, and proficiency, and that could express a lack of differences in conflict resolution in the incongruent condition that requires the use of executive control mechanism. However, it is possible that these behavioral studies (12, 23, 24) are based on the performance of young monolingual and bilinguals, therefore, we must be careful in drawing parallels with the present study where young and older bilinguals varying in L2 usage and proficiency are compared. In sum, behavioral results of the present study confirm previous findings with the ANT, that the early subcomponents of attention—alerting and orienting ability—are a sensitive indicator of age-related differences in L2 matched older and younger adults.

The fMRI results add an important perspective on group differences between young and older bilinguals in the subcomponents of attention. The current study showed an increase in the neurofunctional activation for the alerting and orienting subcomponents of attention for older bilinguals when compared to young bilinguals using disjunction analysis. Specifically, there was a significant activation in the left ventrolateral prefrontal cortex (BA 10) for the elderly bilinguals with alerting trials and a significant activation in the right superior parietal gyrus (BA 39) with the orienting trials. Furthermore, in a region-of-interest analyses for the different subcomponents of attention [predefined areas based on Fan et al. (1)], older adults showed reduced neural activity in the left inferior frontal gyrus (BA 47) with alerting trials, but no significant group difference with orienting and executive control trails in the anterior cingulate, other parietal sites and frontal eye fields.

Neurofunctional patterns in older adults fit well with the previous literature on aging (55, 56), showing that fronto-parietal activity increases with age. This age-related increase in activation was observed concurrently with higher response times on the ANT and working memory tasks (OBT). Specifically, in the elderly, response times to alerting trials on the ANT task were positively correlated with activations of the VLPFC (BA 10). According Cabeza et al. (57), older adults' performance is influenced by an increase in age-related PFC activation, thus confirming the present results. However, we find positive correlation between the response time on the working memory task and the BA 39 activity ($r = 0.454$, $p = 0.004$) indicating increase in working memory performance correlated with reciprocal increase in BA 39 activity. In addition, superior parietal area (BA 39) is reported in literature to play a critical role in covert and overt shift of attention (58) and thereby having a crucial role in attentional shift in space (59). This age-related increase in neural activation in the frontal and parietal areas responsible for the alerting ability also showed corresponding increase in response time for the ANT task performance. Hence, by relating behavioral and BOLD signal changes in the alerting ability, the present work shows that—in comparison to young bilinguals—older bilinguals rely upon the prefrontal cortex (BA 10) to sustain the level of alertness required for the ANT task performance. Also, the positive correlation between response time on the working memory task (One back task) and the activation of the superior parietal gyrus (BA 39) indicates that working memory processing contributes to orienting attention in space. This is in line with previous work showing the role of working memory processes in spatial attention (60). The novelty of the present results relies on the fact that the result shows a correlation between reduced BOLD response in older bilinguals and response times with the alerting and orienting ability, instead of executive control (49, 61). This suggests that age-related differences in the cue-driven performance in the alerting and orienting ability could result from reduced neural efficiency. However, age groups did not differ in regard to the neurofunctional and behavioral patterns of executive control ability, showing significant activations in the left cingulate gyrus (BA 30) and the left middle occipital gyrus (BA 19) for older and young bilinguals, respectively. The lack of result in the disjunction analysis (OA > YA) for the executive control ability can be explained by the fact that both the groups were strictly matched on L2 age of acquisition, usage, and proficiency. This is in line with the previous study (13) that shows comparable neurofunctional activation for the older bilinguals in comparison to the young adults (monolinguals and bilinguals) in executive control ability. Also, the results for young bilinguals on the executive control performance are in line with bilingual anterior to posterior and subcortical shift

hypothesis (BAPSS) (62), that suggest less activation of the frontal brain areas responsible for executive function and greater recruitment of posterior/subcortical regions by bilinguals when compared to monolinguals.

We also explored the possibility that decreased neural efficiency in older bilinguals may vary with L2 variables resulting in cognitive reserve. The results show that neural efficiency—decrease in neural activity—is correlated with increasing L2 proficiency as measured by discourse tasks, thus suggesting that higher L2 proficiency through life-long use of the two languages, contributes to neural efficiency for the alerting ability. Research on bilingualism has mostly focused on comparisons between monolingual and bilingual populations, showing both cognitive and neural advantages in bilinguals (8, 18, 63), accounted by neuroanatomical (17, 64–66) and neurofunctional changes (11, 13–15). The present study is the first one to report on age-related differences on behavioral and neurofunctional patterns of attention in comparable bilingual populations differing in age and varying in L2 usage, and proficiency.

In sum, the evidence showed an increase in the brain activity for the older bilinguals in comparison to young bilinguals in the frontal and parietal areas during alerting and orienting subcomponents of attention and this is correlated with lower L2 proficiency and higher working memory response time across group. According to Wang and Fan (67), alerting ability results in broad sensitivity toward incoming stimuli and this ability reduces with increasing age. In the present study, a bilingual advantage in maintaining this alert state is observed in the elderly bilinguals, and this ability is associated with increasing L2 proficiency on discourse tasks. This is in line with the previous studies supporting bilingual advantage in the cognitive control performance on the continuum of L2 proficiency (68, 69). Together, our results suggest that benefits of lifelong bilingualism might rely specifically upon the alerting subcomponent of attention.

CONCLUSION

Defining and interpreting age-related differences in bilingual population, based on behavioral and neuroimaging data is an ongoing challenge. In this study, we compared older and younger adults, matched on measures of bilingualism and education, to understand the role of bilingualism in aging. A bilingual advantage was observed, specifically in the alerting ability, a subcomponent of attention responsible for establishing a state of alertness for the incoming stimuli. This finding points to alerting abilities as the potential core component of the so-called bilingual attentional advantage.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CIUSSS Aging and Neuroimaging Research Ethics Committee of Center-Sud-de-l'Île-de-Montréal. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TD carried out the data collection, analysis, and interpretation, and drafted the initial article. TD, AA, and YJ participated in the interpretation, discussion, and manuscript preparation. PB contributed to the fMRI design and analysis of the study. All authors read the final manuscript and approved it for publication.

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Correlations of Neuropsychological and Metabolic Brain Changes in Parkinson's Disease and Other α-Synucleinopathies

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Cognitive impairment is a common feature in Parkinson's disease (PD) and other α-synucleinopathies as 80% of PD patients develop dementia within 20 years. Early cognitive changes in PD patients present as a dysexecutive syndrome, broadly characterized as a disruption of the fronto-striatal dopamine network. Cognitive deficits in other domains (recognition memory, attention processes and visuospatial abilities) become apparent with the progression of PD and development of dementia. In dementia with Lewy bodies (DLB) the cognitive impairment develops early or even precedes parkinsonism and it is more pronounced in visuospatial skills and memory. Cognitive impairment in the rarer α-synucleinopathies (multiple system atrophy and pure autonomic failure) is less well studied. Metabolic brain imaging with positron emission tomography and [^{18}F]-fluorodeoxyglucose (FDG-PET) is a well-established diagnostic method in neurodegenerative diseases, including dementias. Changes in glucose metabolism precede those seen on structural magnetic resonance imaging (MRI). Reduction in glucose metabolism and atrophy have been suggested to represent consecutive changes of neurodegeneration and are linked to specific cognitive disorders (e.g., dysexecutive syndrome, memory impairment, visuospatial deficits etc.). Advances in the statistical analysis of FDG-PET images enabling a network analysis broadened our understanding of neurodegenerative brain processes. A specific cognitive pattern related to PD was identified by applying voxel-based network modeling approach. The magnitude of this pattern correlated significantly with patients' cognitive skills. Specific metabolic brain changes were observed also in patients with DLB as well as in a prodromal phase of α-synucleinopathy: REM sleep behavior disorder. Metabolic brain imaging with FDG-PET is a reliable biomarker of neurodegenerative brain diseases throughout their course, precisely reflecting their topographic distribution, stage and functional impact.

Keywords: Parkinson's disease, cognitive impairment, α-synucleinopathies, dementia with Lewy bodies, multiple system atrophy, [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET)

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INTRODUCTION

Parkinson's disease (PD) is a chronic neurodegenerative disease affecting 2–3% of the population older than 65 years. It is primarily a movement disorder characterized by bradykinesia, rigidity, postural impairment, and resting tremor. Its neuropathologic hallmarks are degeneration of substantia nigra and intracellular aggregation of α-synuclein (1). Since James Parkinson's *An Essay on the Shaking Palsy* (2), which still remains largely valid, new knowledge has been gained, particularly on non-motor symptoms, some of which may precede motor signs by decades (3). Cognitive decline, which was not described by James Parkinson, is one of the most debilitating non-motor symptoms and it may drastically decrease patient's and caregiver's quality of life. It is now recognized that the full spectrum of cognitive decline, ranging from subjective cognitive decline (SCD) through mild cognitive impairment (MCI) to dementia can be observed in PD patients (4).

Furthermore, cognitive impairment is important for diagnosis and differential diagnosis among α-synucleinopathies, since some are strongly associated with dementia [PD and dementia with Lewy bodies (DLB)] and others not [multiple system atrophy (MSA) and pure autonomic failure (PAF)]. Although underlying pathology (α-synuclein) is the same in all-aforementioned conditions, its topography, pathophysiology and clinical presentation of cognitive impairment may differ.

Cognitive impairment is a common feature of PD and based on different criteria and thresholds, 10–40% of PD patients have MCI (PD-MCI) at the time of the diagnosis (5–11). Among the PD patients with normal cognition at baseline almost 50% develop MCI within 6 years (12), however around 20% of patients with PD-MCI revert to normal cognition after a year (13). Additionally, subtle cognitive decline, presenting as a decline in the processing speed and executive functions as well as a mild decrease in Mini-Mental State Examination (MMSE) score may even precede PD diagnosis for up to 7 years (14). SCD, which is a risk factor for Alzheimer's dementia (AD), is believed to also precede MCI in PD, and SCD in PD remains an active research topic (4).

Current diagnostic criteria proposed by Movement Disorder Society define PD-MCI as a gradual decline of cognition, not causing a significant impact on a patient's everyday functioning. It is defined by clinical, cognitive, and functional criteria (15). PD-MCI is a heterogeneous disorder and it can be either amnestic or non-amnestic (16). PD-MCI correlates with an increased risk of developing dementia (12, 13, 17). PD dementia (PDD) causes cognitive changes in more than one domain and affects the subject's day-to-day functioning (18). It is a common feature of the disease and, if patients live long enough, it occurs in almost 80% of them within 20 years from the initial diagnosis (19). On the other hand, patients who develop dementia prior or within 1 year of first motor signs of parkinsonism are diagnosed with DLB (20). While DLB and PDD are both characterized by similar pathology and cognitive impairments, e.g., executive function, attention (21, 22), DLB patients perform worse on visuospatial and memory tests (23). Their cognitive decline is faster with more severe fluctuations and their survival-time is shorter (24, 25).

MSA is a less common α-synucleinopathy characterized by autonomic failure, cerebellar and parkinsonian signs and one third of patients develop frontal-lobe dysfunction (26, 27). A minority of MSA patients also develop dementia syndrome, which has a rather heterogeneous clinical presentation (28–30). α-synucleinopathies are commonly preceded by prodromal conditions, such as idiopathic rapid eye movement (REM) sleep behavior disorder (RBD) or, rarer, PAF. RBD, not an α-synucleinopathy by itself (31), is characterized by lack of muscle atonia during REM sleep and it has been shown that RBD patients perform worse on neuropsychological tests compared to healthy controls (32, 33). A big majority of RBD patients also develop α-synucleinopathies; PD, DLB, or MSA (34–37). In PD patients, RBD correlates with a higher prevalence of PD-MCI and its presence predicts cognitive decline at follow-up (38–41). RBD may therefore offer an insight into the development of dementia at its preclinical phase and be an excellent target for disease-modifying interventions. However, reliable and objective biomarkers of progression of cognitive impairment and conversion to dementia are still under development (42). PAF is characterized by α-synuclein inclusions in peripheral autonomic nervous system and consequential autonomic symptoms (43). PAF, similarly to RBD, often progresses to various α-synucleinopathies, although its relation to later cognitive decline is still unclear (44).

The etiology of cognitive impairment in PD can be divided into two partially overlapping orthogonal patterns, according to the dual syndrome hypothesis (45). Cognitive changes in planning ability, working memory and executive function (dysexecutive syndrome) in PD-MCI patients arise due to disruption of the fronto-striatal dopamine network, which is mainly caused and driven by the depletion of striatal dopamine transmission, rather than by primary frontal dysfunction (46). Executive functions are also closely correlated with the mesocortical dopamine system, which arises in the ventral tegmental area and projects to the neocortical areas and whose hyperactivity may act compensatorily in the early PD when only the fronto-striatal system is impaired. There is some evidence that disruption of both dopaminergic systems is necessary for the development of dysexecutive syndrome (45, 46). Disruption of the noradrenergic and cholinergic system further contributes to the executive dysfunction (46). On the other hand, patients who mostly suffer from deficits in visuo-spatial function and semantic fluency, already early in PD course, have marked posterior cortical and temporal lobe dysfunction (45). It has been shown that the latter subgroup of patients develops dementia more rapidly (47). Attention, visuoperceptual, and memory deficits also correlate with the neurodegeneration of the cholinergic nucleus basalis of Meynert and a consequential disruption of the posterior cholinergic network (46).

[^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) is a well-established diagnostic method in early and differential diagnosis of neurodegenerative brain diseases, including dementia (48). FDG enters the cells via glucose transporter, where it is metabolized and stays trapped in the cell, and where ^{18}F decays (49). Although it is still under debate whether FDG signal mainly reflects neuronal or

astrocytic glucose metabolism (50, 51), it is still thought to be a direct measurement of synaptic activity (52) and is in close correlation with cerebral blood flow (53, 54). It was shown that impaired glucose metabolism antecedes atrophy in Parkinson's and Alzheimer's disease and that these two processes represent consecutive changes of neurodegeneration (55, 56), making FDG-PET an excellent candidate for an early disease stage biomarker. As demonstrated by a recent meta-analysis, functional brain abnormalities detected with FDG-PET scan, are more consistently and reliably observed in PD patients than are the structural changes detected with voxel-based morphometry magnetic resonance imaging (MRI) (57). Although the topography of hypo/hypermetabolic changes is thought to be specific for different neurodegenerative disorders (58, 59), FDG-PET information in the clinical setting is only regarded as supportive or not supportive of the diagnostic hypothesis and it is recommended to be always used in addition to clinical and neuropsychological assessment (48).

The last few decades brought us enormous progress in both image acquisition techniques and subsequent FDG-PET image analysis methods. These have broadened our understanding of disease processes in neurodegenerative brain diseases through defining regional disease-related metabolic changes as well as by investigating their long-range consequences on the spatial connectivity and whole brain metabolic changes (60).

Although international guidelines suggest the use of quantitative techniques for aiding the interpretation of brain FDG studies (61, 62), in clinical setting visual assessment of FDG-PET images may still be deemed appropriate, depending on the individual, local procedures. Visual assessment, however, harbor limitation measured by inter-rater variability, mainly depending on the expertise and experience of the reader (63). Assessment by visual reading can be improved by the use of various statistical mapping approaches (64, 65). The use of automated semi-quantification methods is advised by the European Association of Nuclear Medicine and the European Academy of Neurology for increased accuracy of image reading (66). The most widely accepted methods are based on mass univariate testing, such as statistical parametric mapping (SPM) (67, 68). For clinical evaluation, it has been established to apply SPM for voxelwise comparison of e.g., regional FDG uptake of a single patient's image with the age matched control group images, preferentially acquired at the same site. In this approach, each voxel is evaluated independently, without an a-priori hypothesis and voxel clusters that are statistically significantly different, after correction for multiple comparisons, between the patient's and control group's images can be identified and mapped onto an anatomical atlas or an individual, structural MRI for further interpretation (68). Other statistical approaches include multivariate analyses, such as scaled subprofile model/principal component analysis (SSM/PCA). When properly applied, this method can be used to generate specific disease-related patterns (58, 69, 70). Pattern's expression can be prospectively measured and quantified from the individual scans with the Topographic Profile Rating (TPR) analysis (70). For all the methods, however, a basic knowledge of both, disease characteristics and statistical procedures is needed for proper interpretation of the results.

As most neurodegenerative brain syndromes manifest with a range of cognitive impairments, neuropsychological assessments represent the gold standard of its assessment. Metabolic imaging may significantly contribute to our understanding of functional anatomy and pathophysiological underpinnings of cognitive impairments.

The aim of this review was driven by two basic questions: (i) do neuropsychological data in PD and related α-synucleinopathies correlate with metabolic neuroimaging data and (ii) do these neuroimaging data reveal correlates of impaired cognition already in syndromes that are known to predict evolution into PD, DLB, and MSA.

METHODS

A literature search on PubMed was performed using terms: "cognitive," "cognition" or "neuropsychological" and "Parkinson," "Parkinson's," "dementia with Lewy bodies," "DLB," "LBD," "PDD," "Multiple system Atrophy" or "MSA" and "Fluorodeoxyglucose," "Fluoro-deoxyglucose," "FDG," "hypometabolic" and variations, or "hypermetabolic" and variations. Additionally, for our second aim, we included search terms "REM Sleep Behavior Disorder," "RBD," "Pure autonomic failure" or "PAF." Two hundred sixty-four articles were found and analyzed. Only original research articles relevant to the aforementioned rationales and pertaining to human studies, written in the English language, published up to June 2019 were included in this review. Case reports, interventional studies, comparisons with non-α-synucleinopathies, studies investigating non-cognitive signs, etc. were not taken into account.

PARKINSON'S DISEASE

We reviewed studies investigating MCI in PD, its progression to PDD and studies specifically addressing the correlation between metabolic changes and neuropsychological deficits.

Already in 1992, Peppard et al. described that cognitive decline in PD is accompanied by changes in brain glucose metabolism (71). More recent studies focused on cognitive decline in specific stages of PD. In comparison with healthy control (HC) participants, it was shown that PD-MCI patient exhibit regional glucose hypometabolism in temporo-parieto-occipital regions (72–74). The same pattern of hypometabolism, although to a lesser extent, is seen when comparing PD-MCI with PD patients having normal cognition (72, 73, 75, 76), marking posterior, presumably cholinergic disruption. Although, when Lyoo et al. divided PD patients into MCI subgroups, the single domain amnestic subgroup exhibited no differences in comparison to HC (73). Lack of differences may be accounted to small sample size ($n = 12$) and topographic heterogeneity of hypometabolic brain changes in amnestic MCI subgroup. Rather inconsistent are also findings of the frontal metabolic changes in PD-MCI in comparison to HC. Some studies report frontal hypometabolism (72, 73, 76) and the others frontal hypermetabolism in paracentral lobule (75) in PD-MCI patients. This inconsistency can be explained to some degree by selective

focusing on hypometabolic changes in some studies and thus not paying attention to hypermetabolic ones. The hypermetabolic changes however previously rose some controversy regarding their meaning (77–80). Recent results (81–83) show that relative hypermetabolism is a true (compensatory) feature of cognitive changes in neurodegenerative diseases and not just a side-effect of normalization. Furthermore, heterogeneity of PD-MCI sample (84), different image reconstruction algorithms (85) or the selection of a comparison group could also be a source of confounding results. It is also a possibility that mild frontal hypometabolic changes were not seen in a small sample studies due to stringent statistical thresholds. Studies investigating the progression of cognitive decline showed that extensive parietal and occipital hypometabolic changes can predict the development of PDD in PD-MCI patients (65, 86–88) and also in PD patients with normal cognition (88, 89). Changes in glucose metabolism were also shown to be correlated with global cognition changes and other neuropsychological tests (90, 91).

Only few studies investigated the correlation of regional metabolic brain changes with cognitive dysfunction detected by neuropsychological tests.

Deficits of executive functions correlated with frontal hypometabolism in some studies (92, 93), but not in the others (94–96). Furthermore, disruption of the striatal dopaminergic system, shown with [^{18}F]-6-fluorodopa PET imaging, correlated with executive dysfunction in patients with preserved metabolism in the frontal cortex (97), with uncertain explanation. The effect of anti-parkinsonian medication on metabolic changes, which may influence fronto-striatal dopaminergic network (98), has not been thoroughly addressed as of yet. Hypometabolism in parietal and temporal cortices more consistently correlated with executive dysfunction (92–96). Attention deficits, regarded by some as an executive dysfunction (99), correlate with hypometabolism in the frontal cortex (95), precuneus and parietal cortex (94) and with the hypermetabolism in the putamen, parahippocampal gyrus, inferior frontal lobule, paracentral lobule, and hippocampus (94). Posterior cholinergic neurodegeneration, marked by the initial decline in visuospatial functioning and followed by memory impairment, can be detected by glucose metabolism changes, too. The former deficits correlate with the occipito-parietal, temporal and precuneal hypometabolic changes (94, 96), but also with the putaminal and parahippocampal hypermetabolism (94). Memory deficits correlated with the temporal and parietal hypometabolism (92, 94, 95). However, both, hypo- and hypermetabolism in the posterior cingulate cortex were found to correlate with memory deficits (94, 96).

The next paragraph focuses on metabolic network analyzes in cognitive changes in PD. A specific regional metabolic covariation pattern, associated with poor performance on tests of executive control and attentional control of working memory, was identified in non-demented PD patients using the region of interest-based SSM/PCA analysis. It was characterized by increased metabolic activity in the left pallidum and mediodorsal thalamus associated with decreased metabolic activity bilaterally in the ventromedial frontal regions, striatum and in the left hippocampal gyrus (100). Later, a voxel-based adaptation of SSM/PCA was used to identify a specific spatial covariance pattern associated with cognitive functions in PD patients, termed PD-related cognitive pattern (PDCP) (**Figure 1**). PDCP was identified and validated in two groups of non-demented PD patients. Both patient groups were relatively young, 58.6 and 58.8 years, respectively and had a high MMSE score of 28.3 and 28.1, respectively. The magnitude of PDCP expression correlated with a test of executive function (Trail Making Test B), Symbol Modality Test, memory functioning (California Verbal Learning Test) and test of visuospatial function (Hooper Visual Organization Test). This cognitive pattern did not correlate with patients' motor impairment. PDCP is characterized by bilateral hypometabolism in the supplementary motor area, precuneus,

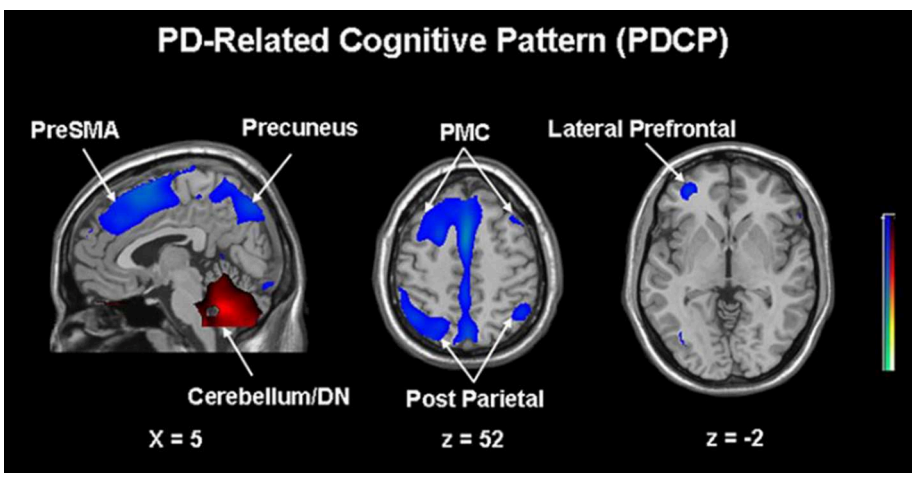

FIGURE 1 | Parkinson's disease-related cognitive pattern (PDCP) identified by scaled subprofile model/principal component analysis (SSM/PCA) from a group of 15 non-demented PD patients. PDCP is characterized by bilateral hypometabolism in the supplementary motor area (preSMA), precuneus, the dorsal premotor cortex (PMC), inferior parietal lobule and left prefrontal region and relative increases in the cerebellar vermis and dentate nuclei (DN). Voxels showing metabolic increases are color-coded red and those showing metabolic decreases are color-coded blue. Reprinted with permission from Huang et al. (101).

the dorsal premotor cortex, inferior parietal lobule and left prefrontal region and relative increases in the cerebellar vermis and dentate nuclei. Furthermore, PDCP has shown to be a robust metabolic indicator of cognitive decline in PD, as its scores were stable in a group of patients which was scanned twice over two months (101). PDCP encompass both posterior and frontal changes as well as compensatory hypermetabolic changes and therefore present a reliable, objective biomarker of cognitive decline. Similarly, another specific brain metabolic network, termed PD-related pattern (PDRP), which correlates with the severity of motor symptoms, was identified prior to PDCP (102). PDCP was later also identified in two different cohorts and the results significantly correlated with the original one (103, 104). Both newly-derived PDCPs also correlated with neuropsychological tests of executive functions (103, 104). Two longitudinal studies showed that the expression of PDCP increases over time, but its expression lags behind the expression of the motor function related PDRP (105, 106). This is in consistence with clinical findings in PD, where motor symptoms precede significant cognitive changes (1). Furthermore, it was shown that PDCP expression is in correlation with the worsening of cognitive impairment (107) and with the loss of dopaminergic input in the anterior striatum, particularly in the caudate nucleus, as shown with dopamine transporter imaging ([^{18}F]-fluoropropyl-β-CIT PET and [^{18}F]-fluorodihydroxyphenylalanine (FDOPA) PET) (108, 109). Hypermetabolic cerebellar changes, once argued to be an artifact (77), have recently been proven a true feature of cognitive decline representing a compensatory activation of cognitive networks including the cerebropontocerebellar tract (81). Since original PDCP was identified in non-demented patients, further studies explored its relationship to other dementia syndromes. Mattis et al. applied TPR algorithm to calculate individual's expression of PDCP and showed that it is not expressed in patients with AD (110). Ko et al. identified a different and specific brain metabolic pattern of cognitive decline in PDD (**Figure 2**). PDD cognition-related pattern was characterized by decreased metabolism in the left caudate nucleus, middle and posterior cingulate gyri, temporal regions, amygdala, hippocampus and midbrain and no metabolic increases were found. This pattern was identified in a group of patients with PDD with an average age of 70.7 years and MMSE score 16.2. PDD cognition-related pattern negatively correlated with MMSE score (111). Its topography is similar but not identical to the PDCP identified in non-demented PD patients. Similar but not the same statistical methods were recently used on resting-state functional MRI data (rs-fMRI). Independent component analysis identified rs-fMRI PDCP (fPDCP), which was topographically similar to its FDG-PET derived counterpart. fPDCP was characterized by reduced regional activity in the precuneus, medial parietal cortex, medial prefrontal and supplementary regions, thalamus and inferior parietal cortex (112). For a more detailed explanation of PDCP, we refer the reader to a recently published review article (113). The detailed table with studies investigating neuropsychological changes in correlation with glucose metabolism in Parkinson's disease is available as a supplementary material (**Table S1**). Future studies may be warranted to investigate the PDCP or fPDCP's ability to detect individuals with worse prognosis of cognitive decline.

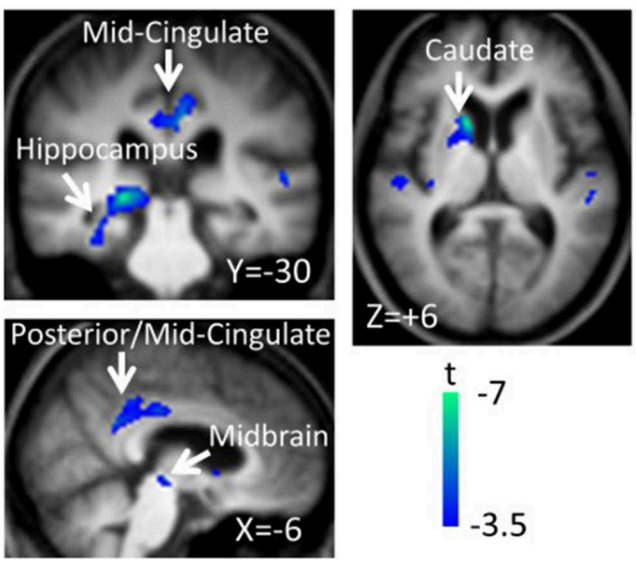

FIGURE 2 | Parkinson's disease dementia (PDD)-cognition related pattern identified by scaled subprofile model/principal component analysis (SSM/PCA) from a group of 18 demented PD patients. Pattern significantly correlated with Mini-Mental State Exam Score ($r = -0.483$, $p = 0.042$). PDD-related cognition pattern is characterized by hypometabolism in the left caudate nucleus, middle and posterior cingulate gyri, temporal regions, amygdala, hippocampus and midbrain and no metabolic increases were found. Voxels showing metabolic decreases are color-coded blue. Reprinted with permission from Ko et al. (111).

MULTIPLE SYSTEM ATROPHY

In general studies investigating metabolic changes in correlation to neuropsychological findings are lacking in MSA. A few studies conducted so far showed consistent hypometabolic changes in frontal cortex, striatum and cerebellum, the latter only in MSA-cerebellar or mixed-type (114–116). As cognitive impairment progresses in multiple domains, hypometabolic changes were not unexpectedly observed in temporo-parietal regions (115). Another group found no correlation between glucose metabolism and MMSE scores (114), but MMSE is probably not sensitive enough to detect cognitive changes in MSA and more detailed neuropsychological testing may be more appropriate in MSA patients.

DEMENTIA WITH LEWY BODIES

In DLB metabolic brain changes are found in temporo-parietal, posterior cingulate, frontal association and primary visual cortex (117–119). A small study (11 patients) from Fujishiro et al. showed that hypometabolism in primary visual cortex can predict DLB in non-demented individuals (120). Furthermore, Sala et al. showed disruption of posterior cortical networks in DLB patients,

especially in the primary visual network (121). Specific disease-related changes in glucose metabolism can be seen in DLB patients even before the development of distinct clinical picture. Early detection of such changes may thus significantly shorten the time to correct diagnosis (122).

Only a few studies directly compared PDD to DLB which are clinically and pathologically similar syndromes and even these with conflicting results. Hypometabolic changes were found in the anterior cingulate cortex in DLB patients in one study (123), while another one found no differences in metabolic topography between DLB and PDD (124). Abovementioned PDD cognition-related pattern was expressed also in DLB patients, though the difference in expression was of borderline statistical significance and there is a need for further exploration of network differences between these two disorders (111).

Awareness of memory impairment was studied on a group of DLB patients and it was found to correlate with hypometabolism in the posterior cingulate cortices bilaterally and the right orbitofrontal cortex (125). Recently, a large multicenter study of 171 DLB patients used whole-brain parcellation approach guided by PCA and followed by linear regression analysis to identify metabolic patterns correlated to the core features of DLB and cognitive decline. Cognitive fluctuations were found to be associated with hypometabolism in bilateral occipital cortices and with hypermetabolism in the parietal lobe. Furthermore, a sensitivity map of the disease severity (measured by MMSE score) was constructed and the posterior cingulate cortex was identified as a region most closely correlated with the decline in MMSE (126).

RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER AND PURE AUTONOMIC FAILURE

RBD is a prodromal phase of Lewy body disorders and even at this prodromal stage metabolic changes pointing toward PD, DLB, or MSA can be seen (40, 127, 128). SSM/PCA network analysis was used to identify RBD-related pattern (RBDRP). It was characterized by increased metabolic activity in the pons, thalamus, precentral gyrus, supplementary motor area, medial frontal gyrus, hippocampus, parahippocampal gyrus, supramarginal and inferior temporal gyrus, and posterior cerebellar tonsils and associated with decreased metabolic activity in the occipital regions, midbrain (red nucleus) and superior/middle temporal gyrus. Interestingly, expression of RBDRP was high in early-stage, but not in late stage PD (129), which hints toward the change in predominant networks involved in diseases as it progresses from RBD to PD. RBDRP was later identified also in a different cohort of patients (130, 131). Surprisingly, the univariate analysis does not reveal increased metabolism in thalamus, supplementary motor area and extensive cerebellar changes (132), meaning that multivariate analyses may detect subtler brain activity changes compared to the univariate ones. The RBDRP's expression was found to be significantly higher in PD-MCI patients than in PD patients without cognitive decline (130) and it correlated with tests of executive function (131). RBDRP's expression may therefore be related to worse cognitive status in individual PD patients. To the best of our knowledge RBDRP's expression has not been investigated in DLB as of yet. But interestingly, there are metabolic differences between DLB patients with and without RBD, with the former having more extensive metabolic decreases throughout the whole brain (119). There are no published studies investigating neuropsychological and metabolic changes in pure autonomic failure.

CONCLUSIONS AND FUTURE PERSPECTIVES

Neuropsychological changes are among the most common and debilitating non-motor symptoms in PD, they are essential for DLB diagnosis and seem to be present in RBD already. FDG-PET brain imaging is a valuable tool to study the underlying mechanism of cognitive dysfunction in PD and other α-synucleinopathies. We may conclude that neuropsychological data in PD and related α-synucleinopathies correlate with metabolic neuroimaging data, although there are some controversial findings in these metabolic-cognitive correlations, which should be further addressed. Similarly so, the differentiation between the causal and compensatory metabolic changes in these disorders.

Although the studies investigating neuropsychological changes and glucose metabolism in PD related α-synucleinopathies are not many and a majority of them are retrospective, results do reveal correlates of impaired cognition already in RBD and those in most cases predicts the evolution into α-synucleinopathies.

Further research effort should be directed toward prospective follow-up studies of these syndromes from their prodromal stages, to be able to capture subtle metabolic brain changes, already before dementia arises. These may become valuable biomarkers of disease progression and/or conversion to dementia. Recent methodological advances brought forth various objective and quantifiable covariance patterns, which consistently and reliably correlate with cognitive changes and may already predict the disease progression. However, future research is needed to validate these disease-related patterns in larger, multicentric cohorts taking into account an important need for standardization of imaging reconstruction and analysis protocols (133).

Furthermore, topics beyond the scope of this review—neuropsychiatric changes, such as apathy, anxiety and depression, which are common in patients with neurodegenerative brain disorders, need to be addressed as well as their impact on patients' cognitive functions and brain metabolism.

Last but not least, new analytical tools, such as deep learning, that are currently under development may be able to pick up complex neurological circuits involved in cognitive

changes in combination with imaging of the neurotransmitter changes that underlie the brain activity changes in PD and other α-synucleinopathies.

AUTHOR CONTRIBUTIONS

MT and ZP conceptualized the paper and provided inputs and edits. MP performed the systematic search of the literature and wrote the first draft, created the table, and finalized the paper.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01204/full#supplementary-material

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Weaker Inter-hemispheric and Local Functional Connectivity of the Somatomotor Cortex During a Motor Skill Acquisition Is Associated With Better Learning

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Recently, an increasing interest in investigating interactions between brain regions using functional connectivity (FC) methods has shifted the initial focus of cognitive neuroimaging research from localizing functional circuits based on task activation to mapping brain networks based on intrinsic FC dynamics. Leveraging the advantages of the latter approach, it has been shown that despite primarily invariant intrinsic organization of the large-scale functional networks, interactions between and within these networks significantly differ between various behavioral and cognitive states. These differences presumably indicate transient reconfiguration of functional connections—an instantaneous process that flexibly mediates and calibrates human behavior according to momentary demands of the environment. Nevertheless, the specificity of these reconfigured FC patterns to the task at hand and their relevance to adaptive processes during learning remain elusive. To address this knowledge gap, we investigated (1) to what extent FC within the somatomotor network is reconfigured during motor skill practice, and (2) how these changes are related to learning. We applied a seed-driven FC approach to data collected during a continuous task-free condition, so-called resting state, and during a motor sequence learning task using functional magnetic resonance imaging. During the task, participants repeatedly performed a short five-element sequence with their non-dominant (left) hand. As predicted, such unimanual sequence production was associated with lateralized activation of the right somatomotor cortex (SMC). Using this "active" region as a seed, here we show that unimanual performance of the motor sequence relies on functional segregation between the two SMC and selective integration between the "active" SMC and supplementary motor area. Whereas, greater segregation between the two SMC was associated with gains in performance rate, greater segregation within the "active" SMC itself was associated with more consistent performance by the end of training. Nether the resting-state FC patterns within the somatomotor network nor their relative modulation by the task state

predicted these behavioral benefits of learning. Our results suggest that task-induced FC changes reflect reconfiguration of the connectivity patterns within the somatomotor network rather than a simple amplification or silencing of its intrinsic dynamics. Such reconfiguration not only supports motor behavior but may also predict learning.

Keywords: motor cortex, motor learning, motor sequence, memory representation, functional connectivity, fMRI—functional magnetic resonance imaging, resting state, task activation

INTRODUCTION

The neural basis of high dimensionality (e.g., a large repertoire of actions that can be performed in various ways) and adaptability of human behavior has been extensively studied with functional magnetic resonance imaging (fMRI) (1, 2). Using this technological approach, the brain-behavior relationships have been primarily investigated by localizing task-activated brain regions, i.e., areas that exhibit significant increases in mean blood-oxygenated-level-dependent (BOLD) fMRI signal during tasks compared to rest or control conditions [for reviews, please see (3, 4)]. Over the past decade, however, there has been an exponential increase in the number of studies investigating spontaneous hemodynamic activity measured at rest with fMRI; that is, while participants lie quietly in the scanner without any explicit task or stimulus. In fact, assessing correlations of BOLD signal between brain regions during this resting state—a method referred as functional connectivity (FC) (5)—has proven to be a valuable technique for mapping functional networks, including the somatomotor system (6–11). A highly synchronized neural activity between distributed brain regions forming functional networks has been repeatedly demonstrated not only at rest but also during various tasks indicating their resilience to the behavioral or cognitive context (12–15). Together with the observation that spontaneous fluctuations in neural activity account for variability in task-evoked activations and associated behaviors (16–18), such findings lend support to the notion that functional networks in the brain are primarily invariant across behavioral states, whereas momentary demands of the environment play only a modulatory role in their intrinsic functions (19). As such, this view suggests that the functional ability and processing capacity of the brain can be inferred based on FC dynamics during the resting state, meaning that these intrinsic dynamics not only reflect unceasing intrinsically synchronized activity patterns, which are constrained by neuro-anatomical connections (20), but they also determine task-evoked activation and behavior (15, 21–25).

Recently, however, it has become clear that, despite the state-invariant, intrinsic organization of the large-scale functional networks, interactions between and within these networks during the task state significantly differ from their interactions during the resting state (26, 27). Such dissociation between the two states is expressed by rather complex pattern of FC changes, even during simple activities such as passive movie watching (26, 28), with some connections being significantly weakened, whereas others strengthened or unchanged. Although these changes are relatively small, in terms of their magnitude, it has been argued that at least some of them reflect reconfiguration of the functional neural connections rather than a simple amplification or silencing of the intrinsic brain dynamics. This idea of rapid reconfiguration is supported by previous work showing that some of the task-induced changes in the individual whole-brain FC patterns are specific to the ongoing task, hence allowing to accurately decode the type of cognitive processing imposed by such task (29, 30). Moreover, some of those transient FC patterns are related to individual differences in performance levels, suggesting that they are relevant to behavior (27, 31–38). Thus, despite a mainly preserved intrinsic large-scale FC topography across behavioral states, some transient changes in FC on a smaller scale, as captured with the BOLD-fMRI signal, may be the ones that grant humans the ability to flexibly adapt their behavior according to the task at hand (13, 14).

Yet, the relevance of task-induced changes in FC to specific behavior and adaptive processes during learning remains elusive. For instance, it has been shown that the FC strength between and within functional networks increases with task complexity, greater attentional demands, and better performance levels (31, 38–40), but may decrease with learning, which would indicate diminished cognitive control and sensory input dependency to enable automaticity (36, 41). It is worth noting that changes in FC are not limited to task-activated regions and may be dictated by the region's functional connectivity profile (i.e., a relative number of within- and between-network connections) (13), and the level of information processing (e.g., primary vs. multimodal associative areas) (42). Specifically, primary sensory and motor circuits have been found to be particularly prone to change their FC patterns when the brain is engaged in the task, as compared to the resting state. However, our current understanding of these dynamics under specific conditions and their potential role in learning is rather limited.

In the current study we sought to assess the extent to which FC of the somatomotor network is reconfigured by the task state and how these changes support motor task execution and learning. The hypothesis that some aspects of learning are associated with the FC of the somatomotor network during the resting state was also tested. To this end, we applied FC analyses to data from the fMRI experiment conducted by Albouy et al. (43), who scanned participants during both the continuous resting state period and a motor sequence task. During the task, participants repeatedly performed a short five-element sequence using their non-dominant (left) hand. Prior to the task, they were asked to memorize the sequence, i.e., five digits in the predetermined order—this amount of information is within the normal working memory capacity (44) and is easily remembered. In that way,

during the task, participants were able to reproduce the sequence continuously in a self-paced manner without relying on any external cue or input. Also, no feedback was provided at any time during the actual performance.

This approach suits well our goal to investigate FC dynamics within the somatomotor network during motor execution and learning for several reasons. First, this version of the motor sequence learning task has been widely used to probe motor executive function, and is thought to engage the somatomotor network in relative isolation from the rest of the brain (31, 38). The segregation of the somatomotor network from other functional networks not only underlies actual motor sequence production, but is also associated with higher performance levels and better learning (23, 31, 41, 45). This suggests that specialized regions within this low-level network may contain dedicated neural populations that encode and represent motor sequences (46–48). Second, the stimulus-free mode of performance and the continuous nature of the task minimize attentional and cognitive load, thereby allowing greater isolation of the endogenous processes within the somatomotor network. This design is also advantageous for separation between the task-evoked activation and task-based FC patterns—an issue that is inherently present during stimulus-driven and event-related paradigms (49). Finally, the unimanual motor sequence production allowed us to compare FC dynamics between the two somatomotor cortices (SMC) that have highly coherent intrinsic activity but are differentially recruited during the task and, therefore, may differentially contribute to learning (50, 51). Such focus on the FC dynamics within the somatomotor network will provide novel insights into the type and level of knowledge represented within this primary circuit—a topic that has been debated for several decades but still remains controversial (46, 48, 52, 53).

Operationally, we refer to increases in FC strength as evidence for greater functional integration and information sharing, whereas decreases most likely reflect more segregated processing. Both processes may act in parallel and operate on multiple spatial scales affecting FC strength between networks, between regions within the same network, or between neural populations within the same region. Some of these changes, however, may also reflect reduction of correlated noise. Animal studies suggest that stimulus-driven noise reduction is a general property of the brain (54). It contributes to overall stabilization of functional circuits when the brain is engaged in information processing but lacks specificity and, by itself, does not improve fidelity of neural encoding (55, 56).

Using a seed-driven approach with the seed ROI within the SMC contralateral to the performing hand (i.e., the "active" SMC), our analyses were primarily focused on changes in FC within this task-activated region itself as well as between the two SMC. In addition, significant changes in FC with the supplementary motor area (SMA)—a region presumably involved in sequence representation across multiple domains (57)—are also reported. Similar to the SMC, the SMA contains somatotopic information (58, 59) and is part of the somatomotor network (11, 15, 60, 61). Specifically, we sought to distinguish between FC dynamics associated with (1) selective engagement of task-relevant neural representations during motor performance (62, 63) and (2) selective stabilization of these representations during practice (64)—two experience-driven processes proposed by animal studies. Clear behavioral consequences of the execution of the motor sequence task provide a reliable basis to assume that changes in FC between the resting and task states will capture reorganization within the somatomotor network relevant to motor performance. It is also well-established that repeated experience with the motor sequence results in faster and more stable performance (46, 47, 52, 65–68), thereby providing reliable and testable behavioral correlates of learning at the level of action execution and action selection (69).

MATERIALS AND METHODS

Ethics Statement

All participants gave their written informed consent to take part in the study, which was approved by the Research ethics board of the RNQ (Regroupement Neuroimagerie Québec). All procedures were in accordance with the approved guidelines and regulations. Participants were compensated for their participation.

Participants

The current report is based on the analyses of data collected during the initial resting state scan and the training session from a previous fMRI experiment published elsewhere (43). The sample included 55 healthy young right-handed (70) volunteers (mean age: 24.1 $\pm$ 3.5 years, 34 females) who were recruited by local advertisements to participate in the study. Participants were included in the study if they reported no history of medical, neurological or psychiatric disease. None of them were taking medications at the time of testing. All participants had a normal quality of sleep, as assessed by the Pittsburgh Sleep Quality Index questionnaire (71) and the St. Mary Hospital questionnaire (72). Also, none of the participants received formal training as a musician or as a typist.

In addition to the above-mentioned exclusion/inclusion criteria, we have also removed some participants' data from the analysis based on their performance. As such, one participant was excluded because his initial performance rate was slower than the group average by more than three standard deviations indicating a significantly lower general ability to use the keypad (participant's and group average time to complete the first three training blocks: 56.34 and 28.94 $\pm$ 8.01 s, respectively). Two additional participants showed very low accuracy levels by the end of training with only six correctly performed and completed sequences or less (out of the 12 repetitions of the sequence) during each of the last three blocks. Five others showed degraded performance levels by the end of training with slower tapping rate during the last than during the first three blocks. Poor accuracy and decreased performance rate below its initial levels by the end of training may indicate loss of interest or attentional biases that are out of the scope of the current study. Finally, one participant had excessive head movements and one participant did not have resting state data. Consequently, a total of 45 subjects, out of 55, were included in the analyses.

Overall Experimental Design

All scanning runs were performed using functional magnetic resonance imaging (fMRI) while participants were lying supine in the scanner. First, participants underwent a resting state scan (6 min 40 sec) keeping their eyes open and looking at the fixation cross. They were asked to remain still and "not to think about anything in particular." In that way, intrinsic activity during the resting state was not affected by the experience with the motor sequence task *per se* (73, 74). Next, while still in the scanner, participants received instructions about the motor sequence task (see below) and were scanned again while being trained on this procedural paradigm.

Motor Sequence Task

The motor sequence task was designed according to a paradigm that has been widely employed to study procedural memories in humans since its development (46) and was programmed in Matlab R2014a (The Mathworks, Inc., Natick, MA) using Cogent 2000 developed by the Cogent 2000 team at the FIL and the ICN and Cogent Graphics developed by John Romaya at the LON at the Wellcome Department of Imaging Neuroscience (http://www.vislab.ucl.ac.uk/cogent_2000.php). Training on this task required participants to tap a five-element sequence of finger movements on a keypad using their non-dominant (left) hand (**Figure 1**). The sequence (4-1-3-2-4) was introduced to participants using the numbers from 1 to 4 that corresponded to the four fingers of their left hand (excluding the thumb) from the index to the little finger, respectively. Participants received a full explicit introduction of the sequence and were asked to memorize it. The training session was initiated only after the sequence was reproduced three times in a row, without any error. During the actual training, participants were asked to look at the fixation cross and to tap the memorized sequence repeatedly "as fast and with as few errors as possible." In case of occasional errors, they were instructed "to continue with the task from the beginning of the sequence." No feedback was provided to the participants about their performance at any time of the experiment. The training session consisted of 14 successive blocks of practice with 60 keypresses within each block, i.e., equivalent to 12 repetitions of the sequence, and 15-s periods of rest between the blocks. Thus, the duration of the training blocks varied between participants as a function of their performance rate. Furthermore, participants developed faster performance rate spending less time to complete each block as training progressed. During the rest periods, participants were instructed to remain still and look at the fixation cross. A change in color of the fixation cross, from red to green and from green to red, indicated the beginning ("GO" cue) and the end ("STOP" cue) of each training block, respectively. Participants' performance was recorded by saving the code-number (i.e., 1, 2, 3, or 4) and time of each keypress.

Behavioral Data Analyses

It has been consistently shown that experience with explicitly known motor sequences is associated with substantial changes in performance rate while the number of errors is extremely low (43, 52, 65, 66, 75). In line with these observations, the number of errors in the current sample of participants was indeed very low with 0.75 ± 0.08 errors per block (mean ± s.e.m.; an error corresponding to all, i.e., one or more, keys comprising one unsuccessful attempt/trial to perform the sequence—the initiation of each trial was determined by the first two elements within the sequence, i.e., 4-1…, and included these and following keypresses till the next trial; all incorrect keys following correctly performed and completed sequences till the next trial were also considered as an error). Therefore, performance levels were assessed using a measure reflecting performance rate, i.e., the time (duration in sec) per block spent executing the motor sequence task (43, 75).

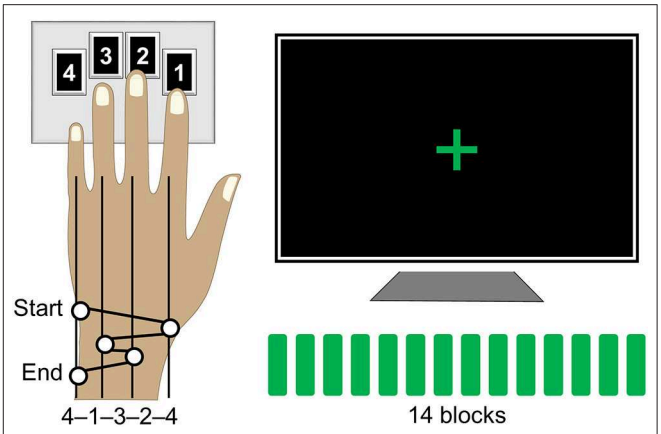

FIGURE 1 | Motor sequence task. Participants were instructed to tap a five-element sequence (4-1-3-2-4) on a keypad using their left hand. The session consisted of 14 successive performance blocks with 60 keypresses each, equivalent to 12 repetitions of the sequence, separated by 15-s periods of rest. During performance blocks, participants were asked to look at the fixation cross and to tap the sequence repeatedly "as fast and with as few errors as possible." A change in color of the fixation cross, from red to green and from green to red, indicated the beginning and the end of each performance block, respectively.

In addition to the development of faster performance, motor sequence learning also involves the formation of a novel tapping rhythm or pattern to generate the same sequence of movements (76). The tapping pattern, which is defined here as the relative temporal spacing between consecutive keypresses, may vary in the beginning but stabilizes by the end of the initial training (75). To assess experience-driven changes in that pattern, we used the same approach as the one published in our previous reports (75, 77). This approach estimates individual changes in the tapping pattern using correlation coefficients, thereby allowing to account for the inter-subject differences in the overall performance rate and the tapping pattern variability (68, 76, 78). To do so, we first extracted inter-keypress intervals, i.e., durations between successive keypresses, within and between all correctly performed and completed sequences separately for each performance block (**Figure 2A**). Next, these intervals were averaged according to their position within and between sequence repetitions in each block; values that were two standard deviations away from their corresponding mean were excluded. This procedure resulted in 14 five-element vectors (one for each block) representing individual tapping patterns of the sequence throughout the

training. Finally, changes in these patterns were assessed using Fisher's *z*-transformed Pearson's correlation coefficients. These coefficients were calculated for blocks 1–13 using the tapping pattern generated during the last block as a reference. Thus, these correlation coefficients indicated the degree of similarity to the tapping pattern formed by the end of training. This measure is sensitive to the relative differences between successive keypresses so that higher values correspond to greater pattern similarity, i.e., greater consistency, and vice versa. However, it does not directly reflect changes in the overall performance rate. Furthermore, the correlation coefficients are sensitive to dynamic changes in the tapping pattern independently of its specific characteristics, such as shape and chunks, allowing valid comparisons at the group level without making any assumption in that regard.

Individual measures, reflecting performance rate and the degree of tapping pattern similarity, were analyzed using Statistical Package for the Social Sciences (SPSS Statistics for Windows, Version 24.0; IBM Corp., Armonk, NY). The analyses were run separately for each measure using repeated measures Analysis of Variance (ANOVA) with *block* as a within-subject factor. The results were corrected for non-sphericity violation using the Greenhouse-Geisser adjustment, when appropriate. We also calculated individual training-related gains in performance rate and the degree of tapping pattern similarity by averaging performance duration and correlation coefficients across the last six blocks. The former values were converted into percents relative to the mean performance duration during the first six blocks to account for inter-subject differences in the initial performance rate. These values were then used as covariates in analyses of functional connectivity patterns (see below).

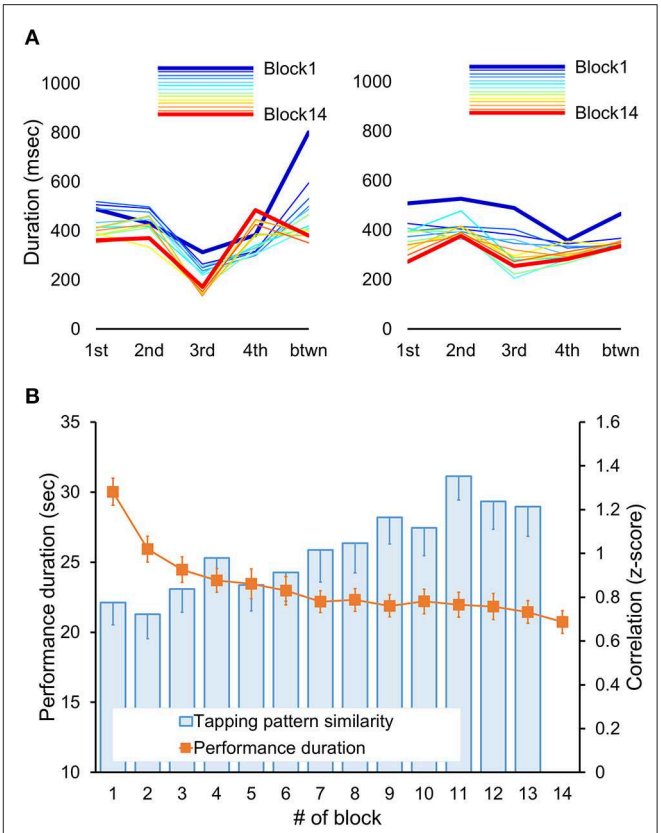

FIGURE 2 | Behavioral results. **(A)** Tapping patterns, i.e., patterns of inter-keypress intervals, for each performance block (Block 1–14) are shown for two representative subjects. Each line connects data points representing mean duration (i.e., inter-keypress interval) for each of four possible transitions between successive elements within a sequence (from 1st to 4th) plus an additional transition between sequences (btwn) for each block. Thus, the shape of each line depicts an individual tapping pattern for a single block. Note, that the initial tapping pattern and its changes throughout the training differed between participants. With practice, the tapping pattern became progressively more similar to the one generated during the last training block (Block 14, red line). Yet, such increased similarity does not necessarily imply faster performance rate. **(B)** Performance duration and degree of tapping pattern similarity averaged across participants are shown for each performance block. The duration of each performance period was assessed in seconds starting from the first keypress following the "GO" cue. The degree of tapping pattern similarity to the tapping pattern formed by the end of training (i.e., during block 14) was assessed based on normalized Pearson's correlation coefficients using the Fisher's z-transformation. These coefficients were calculated for each block (blocks 1–13). Error bars represent standard error of the mean (s.e.m.). Fast improvement in performance speed, as indicated by significant decreases in performance duration across training blocks (orange markers), was also paralleled by significant changes in the tapping pattern so that its similarity to the tapping pattern formed by the end of training significantly increased (blue columns).

fMRI Data Acquisition

The fMRI time-series were acquired using a 3.0 T TIM TRIO scanner system (Siemens, Erlangen, Germany), equipped with a 32-channel head coil. T2*-weighted axial fMRI images sensitive to change in the BOLD signal were obtained with a gradient echo-planar sequence using interleaved acquisition mode in ascending direction (TR = 2.65 s, TE = 30 ms, FA = 90°, FoV = 220 × 220 mm^2, matrix size = 64 × 64 × 43, voxel size = 3.4 × 3.4 × 3 mm^3, 10% inter-slice gap). T1-weighted sagittal 3D MP-RAGE structural images were also obtained (TR = 2.30 s, TE = 2.98 ms, TI = 900 ms, FA = 9°, FoV = 256 × 256 mm^2, matrix size = 256 × 256 × 176, voxel size = 1 × 1 × 1 mm^3).

fMRI Data Preprocessing

Both structural and functional images were converted to the Neuroimaging Informatics Technology Initiative (NIfTI) format using MRIcron (University of South Carolina). Preprocessing of the data was carried out with SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/; Wellcome Trust Center for Neuroimaging, London, UK) operating under Matlab R2014a (The Mathworks, Inc., Natick, MA). Functional volumes were realigned using a least squares approach and a six-parameter (rigid body) spatial transformation to correct for a movement-related variance. Following segmentation and skull-stripping of the structural data, functional images were coregistered to the individual skull-stripped 3-D anatomical image and normalized to the Montreal Neurological Institute (MNI) space using parameters obtained from the segmentation procedure. The normalized functional images were resampled to voxel dimensions of 3 mm^3 and spatially smoothed with an isotropic Gaussian kernel with a full-width at half-maximum (FWHM) of 6 mm to improve the signal-to-noise ratio. Head motion artifact

detection was also applied using the Artifact Detection Tools (79) (normalized z-threshold = 5, movement threshold = 0.9 mm).

Task-Induced Changes in Activity

Task-induced changes in brain activity were assessed on the preprocessed task-related fMRI images using a general linear model (GLM) approach implemented in SPM12. This approach was applied on the preprocessed fMRI images acquired during scanning of the motor task. Statistical analyses of fMRI time-series consisted of a two-stage summary statistics model (80). In the first stage, BOLD signal changes were estimated for each subject using a fixed-effect GLM. A covariate of interest for performance periods was modeled as a boxcar function, time-locked to the onset and duration of each block, convolved with the canonical hemodynamic response function (HRF). Volumes with motion artifacts were ignored using nuisance regression. A high-pass filter of 128 s was used to remove low-frequency noise. Serial correlations in fMRI signal were estimated through a restricted maximum likelihood (ReML) algorithm using a first-order autoregressive plus white noise model. Following parameter estimation, a linear contrast was defined to test the mean effect of performance blocks relative to the rest period.

In the second stage, the resulting individual contrast images (t-maps) were carried forward to the random effects GLM analysis to assess the consistency of the effect between subjects. The statistical inferences were done at the group level using a one-sample t-test. The resulting group activation map was thresholded at $p \leq 0.05$ (two-tailed) using peak-level family-wise error (FWE) correction over the entire brain and overlaid on the mean structural image of all participants using Functional Imaging Visualization Environment toolbox for SPM (FIVE, http://mrtools.mgh.harvard.edu).

Regions of Interest

A main region of interest (ROI), which was also used as a seed for the FC analyses, was defined within the primary somatomotor cortex (SMC) significantly activated during the task as compared to rest. All participants used their left hand to perform the sequence and, therefore, activation within the SMC was strongly lateralized to the right hemisphere. The ROI within this "active" SMC was defined as a sphere ($r = 6$ mm) centered at the nearest local activation maximum to the knob of the precentral gyrus, that is, the motor hand area (81). Due to the close proximity between the motor and somatosensory cortices and their simultaneous activation during the motor sequence task we refer to this region as a somatomotor hand area throughout the manuscript. An ROI within the left ("passive") SMC was also defined in a similar way, in terms of its size and proximity to the hand knob, but using the task-related functional connectivity map of the "active" SMC (i.e., the seed; see below).

Functional Connectivity Analyses

Analyses of functional connectivity (FC) patterns were performed on the preprocessed functional images acquired during the resting and task state using the Functional Connectivity Toolbox (Conn) for SPM (82). FC patterns were assessed using a seed-driven approach.

Prior to the FC analysis, the data underwent additional temporal preprocessing. We applied a component-based noise correction method (CompCor) (83) implemented in Conn to extract five principal components derived from the white matter and cerebrospinal fluid. These components were entered as temporal confounding factors along with the detected volumes with motion artifacts. For the time-series acquired during the training on the motor sequence task, the main effect of performance blocks convolved with the canonical HRF and the corresponding first-derivative terms were included as additional confounds. All confounding factors were removed from the time-series using linear regression. Finally, the resulting residual BOLD time series were also high-pass filtered (0.008 Hz < f).

Individual maps of FC patterns were generated by analyzing the resting state time-series (6 min 40 s, 150 volumes) and the time-series acquired while participants were performing the motor sequence task, separately. The overall time spent on actual performance varied between participants as a function of their performance rate. On average, they spent 5 min and 25 s (123 volumes) practicing the sequence; the total performance time of the fastest and slowest participant being 3 min 42 s (84 volumes) and 10 min 15 s (232 volumes), respectively. The performance periods were separated from the interleaved periods of rest by including a regressor related to performance blocks. To take into account the hemodynamic delay, this regressor was convolved with a canonical HRF and rectified. Thus, the task-based FC analyses were performed on the data acquired during continuous periods of actual performance leaving out the rest. In that way, FC measures reflected interaction between brain regions during the task state that was separated from the task-evoked activation (i.e., global changes in signal from rest to task and vice-versa) or signal fluctuations during interleaved periods of rest.

FC analyses were performed using the ROI within the "active" SMC as a seed. Individual FC maps were generated by estimating Fisher's z-transformed Pearson's correlation coefficients between the BOLD signal averaged across voxels within the seed region and that at every voxel in the brain.

The individual maps were introduced into a second level GLM analyses to obtain group-level estimates. The statistical inferences of the resting state and task-based FC patterns were done at the group level using a one-sample t-test. Task-induced changes were assessed by contrasting statistical maps between the two states ([Task state]—[Resting state]). The resulting maps were thresholded at $p \leq 0.001$ (two-tailed) and overlaid on the mean structural image of all participants using FIVE. For the 3D visualization, maps were projected on the inflated mean cortical surface of all participants using a surface display implemented in Conn.

Regression Analyses

In addition to the second-level analyses to obtain the group-level estimates described above, regression analyses with individuals' behavioral measures as covariates of interest were also performed. This approach allowed us to test for regions where FC strength with the "active" SMC was associated with individual training-induced changes in performance. These analyses were run separately for each performance measure (i.e., gains in

performance rate and the degree of tapping pattern similarity) using the task-based FC maps. Possible relationships between the behavioral measures and the FC during the resting state, as well as its relative changes induced by the task state were also tested. Statistical inferences were made at the peak-level using family-wise error correction (FWE) over a small volume of interest. The volumes of interest were defined as spheres (r = 10 mm) around a center of each ROI. Statistics for clusters that survived a cluster-level extent threshold of $p < 0.05$ following a peak-level threshold of $p < 0.005$ (two-tailed) is also reported. The specificity of associations between FC values and learning measures to the behavioral state was tested as *post-hoc* comparisons between correlations from dependent samples using an online calculator (https://www.psychometrica.de).

RESULTS

Behavioral Results

The time to complete each training block (i.e., performance duration) and the degree of tapping pattern similarity to the one attained by the end of training are shown in **Figure 2B**. Training-related changes in performance were assessed using repeated measures ANOVA with *block* as a within-subject factor. As expected, training on the motor sequence task led to a faster performance as indicated by a significant effect of *block* [$F_{(6.70, 294.43)} = 53.49$, $p < 0.001$]. On average, performance duration decreased from 30.03 ± 0.97 to 20.73 ± 0.814 s (mean ± s.e.m. of the first and the last training block, respectively). These robust gains in performance rate were paralleled by significant changes in the subjects' tapping pattern as indicated by a significant effect of *block* [$F_{(5.92, 260.31)} = 4.76$, $p < 0.001$] on the correlation coefficients between the tapping patterns of the last training block and each of the other training blocks. The degree of similarity to the tapping pattern generated during the last training block increased from 0.78 ± 0.10 to 1.21 ± 0.14 (mean ± s.e.m., Fisher's z-transformed correlation coefficients for the first and penultimate training block, respectively). Thus, practice on the motor sequence resulted not only in faster task execution, but also in the formation of a new, presumably more efficient, pattern for generating the motor sequence.

Task-Induced Changes in Activity

Task-induced changes in activity are shown in **Figure 3**. As expected, task-evoked activation was strongly lateralized to the right SMC contralateral to the performing (left) hand with no significant activation of its homolog within the left hemisphere. Cortical activations were also observed within the supplementary motor area (SMA) as well as in the dorsal premotor and parietal regions, bilaterally.

Task-Induced Changes in Functional Connectivity

Task-induced changes in FC were assessed using a whole-brain functional connectivity analysis approach with the ROI within the "active" SMC as a seed. Comparison of the FC patterns between the resting and task states revealed that during the task the FC strength within the somatomotor network encompassing bilateral somatosensory and motor cortices significantly decreased (**Figure 4**). These decreases were evident not only in the FC estimates between the two hemispheres but also within the "active" hemisphere contralateral to the performing hand. Specifically, FC values between the two ROIs within the somatomotor hand areas during the task state were significantly lower than during the resting state (**Figure 4**, left plots), indicating task-induced functional segregation between the two SMC. These decreases reflected only a relative decline in FC between the "active" and "passive" SMC, as indicated by FC values significantly greater than zero during either state ($t > 17.43$, $p < 0.001$). The preserved functional connections between the two SMC during unimanual task are in line with the resilience of intrinsic brain networks to momentary demands of the environment (19). The significant task-induced decreases in the FC strength were also observed within the "active" somatomotor hand area itself, despite the increased task-induced activation of this primary region. Such suppressive effect of the task state on the FC strength within the "active" SMC may derive from selective synchronization and amplification of activity within neural populations that are better suited to elicit the desired action, thereby locally segregating them from other task-irrelevant units within the same ROI. These changes in the FC strength within the "active" SMC were statistically robust, yet, relatively small, in terms of their magnitude, as compared to the particularly high FC values across the two states (mean ± s.e.m: 1.54 ± 0.04 and 1.26 ± 0.03, for the resting and task state, respectively) (**Figure 4**, right plots), indicating strongly synchronized intrinsic activity between neural populations representing the performing hand. This relative decline in FC strength with the "active"

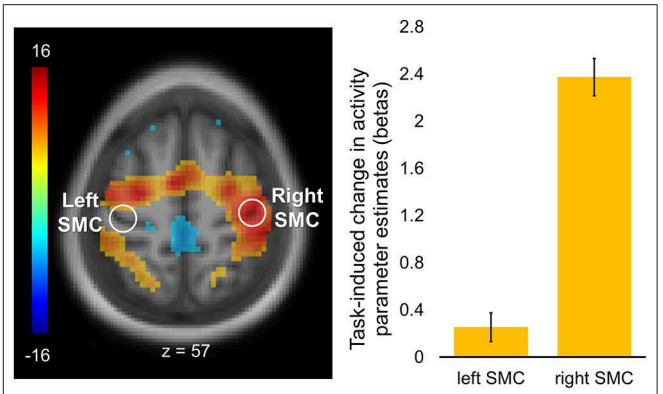

FIGURE 3 | Regions of interest and task-induced changes in activity. A statistical map of the whole-brain analysis of task-induced changes in activity was thresholded at $p < 0.05$ (two-tailed) using peak-level family-wise error (FWE) correction over the entire brain. The map is displayed over the mean structural image of all participants. Color bar represents t values with yellow-red and green-blue shades indicating regions with task-induced activity increases and decreases, respectively. Regions of interest (ROIs, white circles) were defined as spheres (r = 6 mm) within the hand area of the left ("passive") and right ("active") somatomotor cortex (SMC; xyz = −36, −24, 57, and xyz = 42, −21, 57, respectively). Columns represent group mean of task-induced increases in activity for each ROI. Error bars represent standard errors of the mean (s.e.m.).

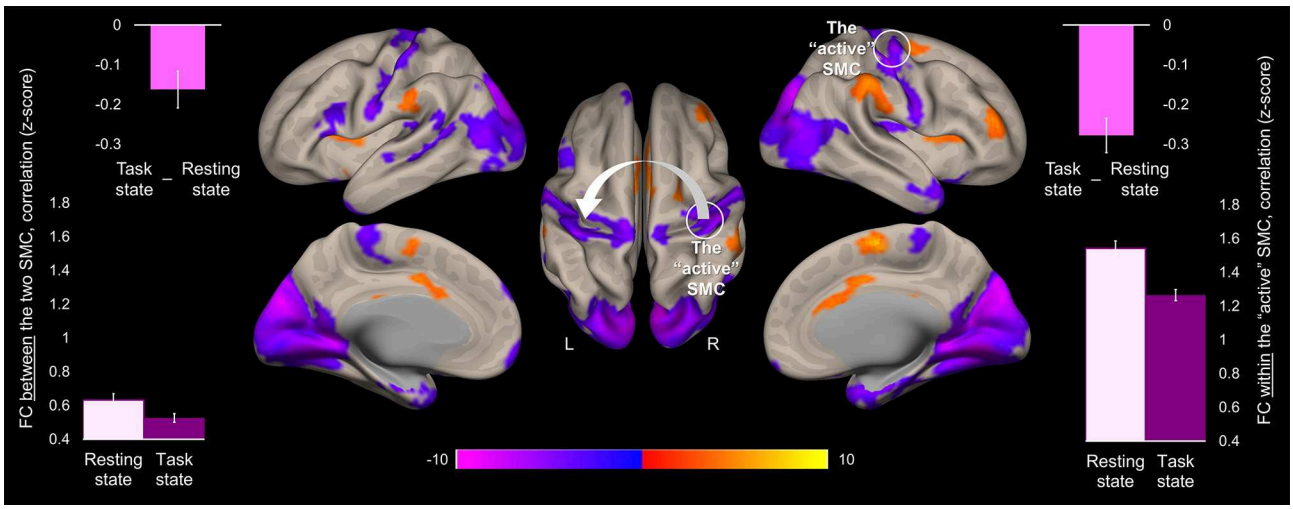

FIGURE 4 | Task-induced change in the whole-brain functional connectivity of the "active" somatomotor cortex. The results of the whole-brain analysis are showing regions where FC with the hand area of the "active" SMC significantly changed during the motor sequence task comparted to the resting state ([Task state]—[Resting state]). The analysis was performed using the ROI within the "active" SMC as a seed (the white circle). The statistical map is displayed over the inflated mean cortical surface of all participants at $p < 0.001$ (two-tailed). A horizontal color bar represents t values with red-yellow and blue-magenta shades indicating task-induced stronger and weaker FC with the "active" SMC, respectively. L and R—left and right hemisphere, respectively. The values of the FC between the two SMC (the white arrow) and within the "active" SMC (the white circle) were extracted separately from the resting and task state time-series (lower left and right plot, respectively); the task-induced decreases in the FC strength between the two SMC and within the "active" SMC are also plotted (upper plots). Columns represent group means. Error bars represent standard errors of the mean (s.e.m.). SMC, somatomotor cortex.

SMC extended beyond the somatomotor hand areas and was widespread along both central sulci. Additional decreases were observed within the occipital lobe, bilaterally. In parallel, the task state resulted in stronger FC between the "active" SMC and higher-level parietal, temporal and prefrontal cortical areas, including the SMA, indicating the need to integrate information from these regions to meet the task goals. Increased FC was also observed within the basal ganglia, including bilateral putamen and thalamus.

Segregation Within the Somatomotor Network and Learning

We next explored the relationship between FC patterns of the "active" SMC and the effect of learning. To this end, the reduction in block duration when performing the task, as a measure of gains in performance rate, and the degree of tapping pattern similarity by the end of training, as a measure for performance consistency, were calculated for each individual. These measures were entered as covariates of interest in the whole-brain FC analyses using the "active" SMC as a seed (**Tables 1, 2**).

Significant effects within the somatomotor network were observed only when the correlation analyses were performed on the task-based FC maps; no significant correlation was evident with FC estimates within the somatomotor network during the resting state either with their relative changes when comparing between the two states (brain regions that exhibited significant effect are listed in **Table 1**). Specifically, during the task, individual differences of gains in performance rate were associated with weaker FC of the seed ROI (the "active" SMC) with its homolog in the left hemisphere (**Figure 5**, right panel; **Table 1.3**). Importantly, despite the fact that the analysis was conducted across the entire brain, the significant effect was notable only around the hand knob. This result may indicate that reduced influences of somatomotor representations of the passive hand on ongoing activity of somatomotor representations of the active hand facilitated the development of faster performance rate. Individual differences in the degree of tapping pattern consistency, on the other hand, were associated with weaker FC within the "active" somatomotor hand area itself (**Figure 6,** right panel; **Table 2.3**). A similar association was found with FC values between the seed ROI and SMA. These results link more consistent performance by the end of training with segregation processes within the "active" SMC and, presumably, its selective information integration with the SMA. Note that all associations were negative (i.e., individuals with greater gains in performance rate and greater consistency by the end of training had reduced seed-based FC within the somatomotor network) and specifically present during the task state (see **Table 3** for detailed statistics of correlation analyses) but not during the resting state (see also left graphs in **Figures 5**, **6**). The direct comparison between correlations resulted in significant effect of state ($z > 2.53$, $p < 0.01$), confirming that the relationship between FC values and learning measures differed between the resting and task state. The significant difference between the two states suggests that FC patterns within the somatomotor network were reconfigured during the task. Only these reconfigured patterns predicted individual differences in learning.

As the results reported above suggest, the two SMC were functionally segregated during the task as compared to the resting state (**Figure 4**). The task-induced segregation, as reflected in

TABLE 1 | Areas where functional connectivity correlated with gains in performance rate.

		MNI coordinates			Peak-level statistics		Cluster-level statistics	
Label		**x**	**y**	**z**	***z*-score**	***p***	**# of voxels**	***p***
1. TASK STATE—RESTING STATE								
A. Positive correlation								
No areas with significant effect								
B. Negative correlation								
							82	0.002
Frontal_Sup_Medial	L	−6	66	3	4.132	<0.001		
Frontal_Med_Orb	R	6	54	−9	3.632	<0.001		
							33	0.029
Temporal_Pole_Mid	L	−36	9	−45	3.875	<0.001		
Temporal_Pole_Sup	L	−30	15	−33	2.963	0.002		
							57	0.006
Temporal_Mid	L	−60	−15	−18	3.718	<0.001		
Temporal_Inf	L	−57	−21	−24	3.226	<0.001		
2. RESTING STATE								
A. Positive correlation								
							40	0.028
Frontal_Med_Orb	L	−9	57	−3	3.831	<0.001		
Frontal_Sup_Medial	L	−6	66	0	3.115	<0.001		
B. Negative correlation								
							84	0.003
SupraMarginal	R	69	−42	27	3.552	<0.001		
Temporal_Sup	R	69	−45	18	2.976	0.002		
3. TASK STATE								
A. Positive correlation								
No areas with significant effect								
B. Negative correlation							13	0.137
Postcentral								
*left SMC (xyz = −36, −24, 57)	L	−36	−27	54	3.263	0.046 $_{FWE*}$		

Functional connectivity analyses were performed for the whole-brain using the right sensorimotor cortex as a seed. Gains in speed were included as a covariate of interest. The resulted maps were thresholded at $p < 0.005$ (two-tailed). The inferences were made at the peak-level using family-wise error correction (FWE) over a small volume of interest. Volumes of interest were defined as spheres (r = 10 mm) around center coordinates of the regions of interest within the hand area of the somatomotor cortices (SMC) and supplementary motor area (SMA) (*). Clusters that survived a cluster-level extent threshold of $p < 0.05$ are also reported. Cluster labeling was performed using AAL (84).

the reduced FC strength, was also evident within the "active" SMC itself. Did the suppressive effect of the task state on the FC strength extend to the somatomotor representations linked to learning? If so, does such effect indicate functional segregation or merely an overall reduction of noise correlations—a phenomenon suggested by animal studies that may lead to a widespread reduction in connectivity strength at the level of neural populations (54)? To answer these questions, we performed correlation analyses on the individual FC values extracted from clusters (peak voxels) where decreased FC with the seed (i.e., the ROI within the "active" SMC) was associated with learning; these clusters are shown in **Figures 5**, **6**. During the resting state, participants who showed stronger FC within the "active" SMC itself, also showed stronger FC between the two SMC ($r = 0.38$, $p = 0.01$) (**Figure 7**, left plot). However, no significant correlation between these estimates of intra- and inter-hemispheric interactions was observed during the task state ($r = 0.10$, $p = 0.51$) (**Figure 7**, right plot). This finding, which indicates that relationship between the intra- and inter-hemispheric interactions differed between the two states, rules out the possibility that suppressive effect of the task state on the FC strength within the somatomotor network can be fully explained by the overall noise reduction. Instead, it suggests that ongoing activity within the "active" and "passive" SMC became less synchronized during the task compared to the resting state and thereby indicates task-induced segregation. This segregation was specifically present between somatomotor representations in each hemisphere linked with different aspects of learning.

The same analysis performed on the individual FC values of the seed ROI with the peak of the significant clusters within the "active" SMC and SMA showed an inverse relationship. No significant correlation between these values was observed during the resting state ($r = 0.18$, $p = 0.25$). However, during the task state, participants with stronger FC within the "active" SMC itself also showed stronger FC between the seed ROI and SMA ($r = 0.45$, $p < 0.01$). This finding indicates that ongoing

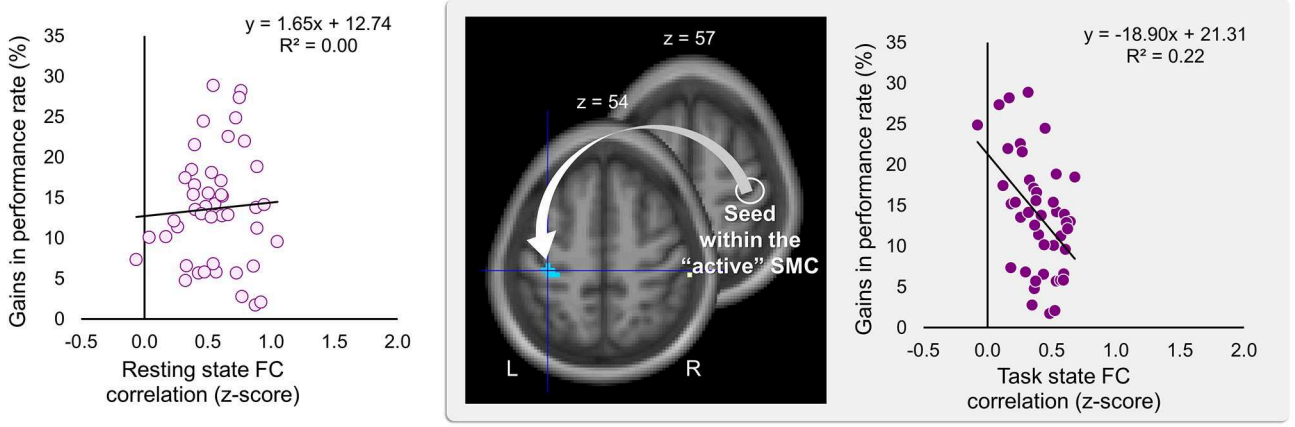

FIGURE 5 | Inverse relationship between individual differences in performance gains and task-based FC strength between the two somatomotor cortices. Gains in performance rate during the training were negatively correlated with the degree of the task-based functional connectivity (FC) between the two somatomotor cortices (SMC). The whole-brain FC analysis was performed on the task state time-series using the ROI within the "active" SMC as a seed (the white circle); individual gains in performance rate were entered as a covariate of interest (middle panel). These gains were calculated as a percentage change in mean performance duration during the last six vs. the first six blocks of training—higher values indicating greater improvement. Gains in performance rate are plotted against FC values extracted from the resting and task state time-series (left and right plot, respectively). The FC values were calculated between the ROI within the "active" SMC and the peak voxel of the significant cluster within the left somatomotor hand area (xyz = −36, −27, 54) (the white arrow). The cyan blob resulted from the statistical maps thresholded at $p < 0.005$ (two-tailed). L and R—left and right hemisphere, respectively.

activity of the specific neural populations within the "active" SMC and SMA, whose FC patterns during the task were inversely related to more consistent performance by the end of training, was also stronger synchronized during the task but not during the resting state.

Differences in Performance Rate as a Possible Confound

The overall time spent on the actual task performance varied between participants as a function of their performance rate so that faster performers spent less time on the task than slower performers. Therefore, it is possible that the current pattern of results might be confounded by the inter-individual variation in the length of the time series used to estimate the task-based FC. However, neither the gains in performance rate nor the degree of the tapping pattern consistency by the end of training were significantly correlated with the individuals' time spent on the actual task performance ($|r| < 0.20$, $p > 0.18$). Therefore, the possibility that the current pattern of results can be fully explained by the differences in the overall performance rate or the length of the time series is unlikely.

DISCUSSION

In the current study, we investigated how functional connectivity within the somatomotor network is reconfigured during a unimanual motor sequence task, and how these changes are related to individual learning capacities. To do so, we applied seed-driven functional connectivity analysis to fMRI data collected in a previous study (43). Participants were scanned during resting state, as well as during a motor sequence task, which required them to repeatedly generate a five-element sequence using their non-dominant hand. Our results suggest that unimanual performance of the motor sequence relies on functional segregation between the two SMC and selective integration between the SMC engaged in the task and the SMA. We thus provide supportive evidence to the notion that task-induced changes in FC reflect reconfiguration of the connectivity patterns within the somatomotor network rather than a simple amplification or silencing of its intrinsic dynamics. Such reconfiguration, as captured with the BOLD-fMRI signal, not only support motor behavior but may also predict learning capacity.

The Widespread Task-Induced Reduction in Functional Connectivity

Here we show that the unimanual motor sequence task induced significant reduction in the FC of the "active" SMC with extensive regions along the central sulcus, bilaterally. Such suppressive effect of the task state on the FC strength is consistent with previous studies that also compared FC patterns between the resting and task states and reported task-induced FC decreases within the somatomotor network (13, 28, 85). However, these within-network decreases were observed across various paradigms, including passive movie watching (28), thereby raising the possibility that FC suppression within the somatomotor network characterizes transitions between brain states (i.e., from the resting to task state) but may not reflect specific processes related to motor action. Moreover, previous findings suggest that the suppressive effect of the various tasks on the FC strength extends beyond the somatomotor network and may be a core feature of local brain circuits regardless of their

TABLE 2 | Areas where functional connectivity correlated with the tapping pattern consistency.

		MNI coordinates			Peak-level statistics		Cluster-level statistics	
Label		**x**	**y**	**z**	***z*-score**	***p***	**# of voxels**	***p***
1. TASK STATE—RESTING STATE								
A. Positive correlation								
							56	0.006
Cerebelum_6	R	30	−54	−36	4.005	<0.001		
Cerebelum_Crus1	R	30	−63	−36	3.825	<0.001		
							43	0.015
Frontal_Sup_Medial	R	6	33	57	3.873	<0.001		
B. Negative correlation							32	0.031
Precentral	L	−30	−3	48	4.076	<0.001		
2. RESTING STATE								
A. Positive correlation								
							112	<0.001
Frontal_Sup_Orb	R	12	72	−3	4.550	<0.001		
Frontal_Med_Orb	L	−3	69	−3	3.859	<0.001		
							65	0.007
Precuneus	L	−12	−60	42	4.110	<0.001		
Parietal_Inf	L	−33	−57	45	3.593	<0.001		
B. Negative correlation								
							121	<0.001
Cerebelum_6	R	30	−54	−36	4.798	<0.001		
Cerebelum_Crus1	R	24	−66	−36	4.327	<0.001		
Cerebelum_8	R	15	−69	−36	3.324	<0.001		
							51	0.015
Cerebelum_Crus1	L	−33	−57	−39	3.394	<0.001		
3. TASK STATE								
A. Positive correlation								
							204	<0.001
SupraMarginal	R	57	−45	33	4.274	<0.001		
Angular	R	57	−57	36	3.185	<0.001		
Parietal_Inf	R	57	−42	48	3.894	<0.001		
Temporal_Sup	R	45	−42	3	4.168	<0.001		
							38	0.017
Angular	R	39	−72	42	4.141	<0.001		
							57	0.005
Temporal_Inf	L	−42	9	−39	3.348	<0.001		
							40	0.015
Occipital_Mid	R	30	−90	15	3.459	<0.001		
B. Negative correlation								
Postcentral							18	0.083
*right SMC (xyz = 42, −21, 57)	R	33	−21	57	3.796	0.009_{FWE*}		
							44	0.011
Supp_Motor_Area	L	−15	0	54	3.540	<0.001		

Functional connectivity analyses were performed for the whole-brain using the right sensorimotor cortex as a seed. The degree of the tapping pattern consistency was included as a covariate of interest. The resulted maps were thresholded at $p < 0.005$ (two-tailed). The inferences were made at the peak-level using family-wise error correction (FWE) over a small volume of interest. Volumes of interest were defined as spheres ($r = 10$ mm) around center coordinates of the regions of interest within the hand area of the somatomotor cortices (SMC)(*). Clusters that survived a cluster-level extent threshold of $p < 0.05$ are also reported. Cluster labeling was performed using AAL (84).

network affiliation, functional properties or cognitive demands of the task (31, 86, 87).

Indeed, the widespread task-induced reduction in FC strength reported by fMRI studies may reflect a global suppression of noise correlations. Such interpretation is in line with the results from animal research that has shown attenuation in correlated variability of neurons' firing rate, which is commonly considered as noise, upon various stimuli and task events (54, 55, 88). This effect was observed across different neural populations regardless of their tuning properties lending support to the notion that the suppression of neural variability may be an overall feature of the cortical response to the task state (54). At the network level, such reduction of noise implies that functional circuits become more stable when driven by stimulus or task.

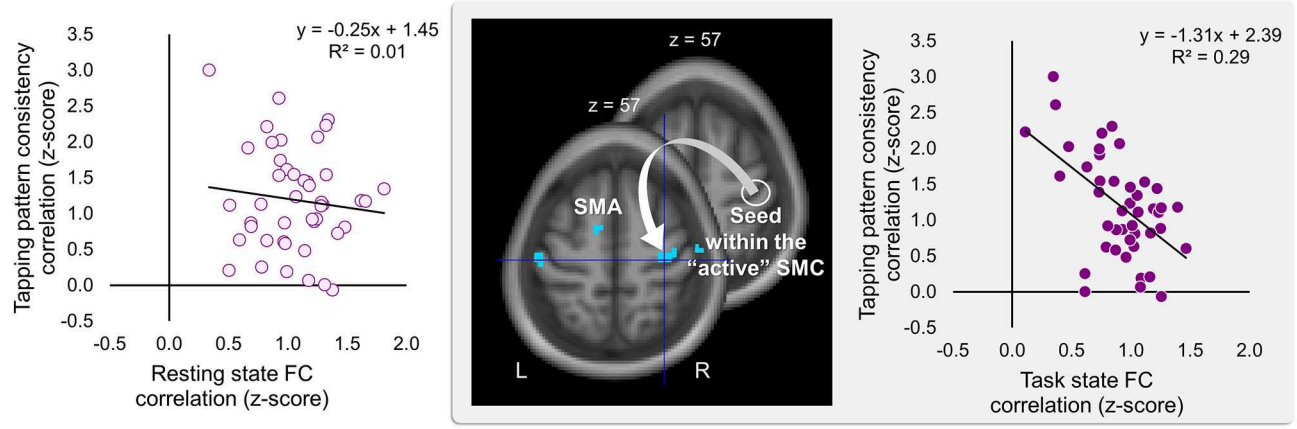

FIGURE 6 | Inverse relationship between individual differences in degree of the tapping pattern consistency attained by the end of training and task-based FC strength within the "active" somatomotor cortex. The degree of consistency in the tapping pattern by the end of training was negatively correlated with the degree of the task-based FC within the hand area of the "active" somatomotor cortex (SMC) as well as between this region and the supplementary motor area (SMA). The whole-brain FC analysis was performed on the task state time-series using the ROI within the "active" SMC as a seed (the white circle); individual measures of the tapping pattern consistency were entered as a covariate of interest (middle panel). The degree of the tapping pattern consistency was assessed by averaging normalized Pearson's correlation coefficients between the tapping patterns generated during the last six blocks excluding block 14 (i.e., blocks 8–13) and the tapping pattern formed by the end of training (i.e., during block 14)—higher values indicating greater tapping pattern similarity and, therefore, greater consistency by the end of training. These coefficients are plotted against FC values extracted from the resting and task state time-series (left and right plot, respectively). The FC values were calculated between the ROI within the "active" SMC and the peak voxel of the significant cluster within the somatomotor hand area (xyz = 33, −21, 57) (the white arrow). The cyan blobs resulted from the statistical maps thresholded at $p < 0.005$ (two-tailed). L and R—left and right hemisphere, respectively.

TABLE 3 | Correlations between the FC strength and behavioral correlates of learning.

	Resting state		Task state		Correlations' comparison between the states	
	r	*p*	*r*	*p*	*z*	*p*
Gains in performance rate in association with:						
FC with the "passive" SMC	0.58	0.71	−0.47**	0.001	2.53*	0.006
Tapping pattern consistency in association with:						
FC within the "active" SMC	−0.11	0.47	−0.54**	<0.001	2.56*	0.005
FC with the SMA	−0.003	0.99	−0.51**	<0.001	2.69*	0.004

*Significant results at 0.01 level; **Significant results at 0.001 level.

Nevertheless, the reduction of correlated noise lacks specificity and, by itself, does not improve fidelity of neural encoding (55, 56). If, however, the noise reduction is correlated with the task-relevant signal, it could improve encoding accuracy and facilitate learning (89, 90).

Reduction in Functional Connectivity and Selective Engagement of Task-Relevant Neural Representations

As predicted in the current study, the task-evoked activation within the somatomotor hand area was lateralized to the hemisphere contralateral to the performing hand [e.g., (2, 91–93)], in line with the known phenomenon of lateralization of somatomotor representations specifically tuned to movements generated by contralateral body parts (94). Given the well-defined somatotopic organization of these representations along the central sulcus, here we argue that the widespread and local task-induced reduction in FC with the "active" SMC may reflect different neurophysiological processes. Specifically, the suppressive effect of the task state on FC strength between the two SMC may derive from the overall non-selective suppression of spontaneous activity to reduce noise correlations. Such noise reduction may also explain task-induced decreases in FC between the seed ROI within the "active" SMC and somatomotor representations of other body parts. The FC suppression within the "active" somatomotor hand area itself, however, may further reflect selective co-activation of neural populations that are particularly tuned to perform the finger tapping task, thereby segregating them from other intrinsically connected, but task-irrelevant units. Supporting fMRI evidence of non-selective decreases in local FC driven by a finger tapping task has been provided by Lv et al. (95), who showed that both fast and slow finger tapping rates have a similar suppressive effect on local FC in the SMC ipsilateral ("passive") to the performing hand. The effect observed within the contralateral ("active") SMC, however, was different, such that the faster tapping rate, which usually results in stronger activation of this region (96–98), was associated with greater reduction in its local FC, hence indicating a greater segregation. Thus, the combination of increased task demands, the stronger activation and the more segregated activity within the contralateral SMC support the idea that FC dynamics within the "active" somatomotor hand area observed in our study constitute a signature for selective

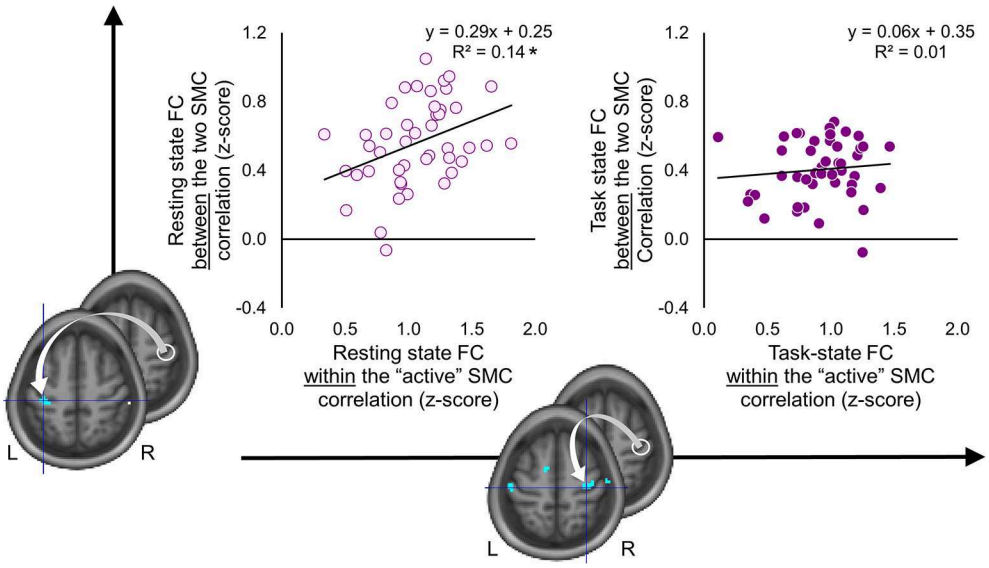

FIGURE 7 | Task-induced segregation between the two somatomotor cortices. Individual functional connectivity (FC) values between the two somatomotor cortices (SMC) (vertical axis) are plotted against FC values within the "active" SMC (horizontal axis) during the resting and task state (left and right plots, respectively). The FC values were calculated between the ROI within the "active" SMC (white circle) and peak voxels of clusters resulted from the whole-brain FC analyses, which were conducted using behavioral measures as covariates of interest (for details see **Figures 5**, **6**). L and R—left and right hemisphere, respectively. *significant correlation at 0.01 level. During the resting state, FC between the two SMC was positively correlated with FC within the "active" SMC. No such relationship was observed during the task state.

engagement of task-relevant neural representations during motor task execution.

The idea of selective engagement of task-relevant neural representations resonates with the emerging recognition that task-induced changes in FC reflect rapid reconfiguration of functional connections (26, 27, 42). Evidently, these changes are relatively small, in terms of their magnitude, as they are probably constrained by mainly invariant large-scale functional brain network topography (13, 14). Nevertheless, some characteristics of such changes are specific to the task at hand, allowing to accurately decode the task state of a participant (29, 30), and are linked to better performance (27, 31–38). Notably, weaker correspondence between FC patterns during the resting and task states particularly characterizes primary sensory and motor circuits (42). Such deviation from the intrinsic brain dynamics may depend on attentional state, stimulus properties, and task complexity (27, 35, 42, 99), hence supporting the idea that transient sub-networks within the sensory and motor circuits are formed to process incoming information or carry out the desired action. Here we show that reconfigured FC patterns within the somatomotor network are not only behaviorally relevant, but may also support learning. In fact, better learning, which was expressed as a faster and more consistent performance by the end of training, was related to individual differences in the FC strength during the task, but not during the resting state. Such dissociation is consistent with the "idling" view on the intrinsic brain function during the resting state (26) and suggests that reconfigured FC patterns within the somatomotor network during the task can capture the neural dynamics that sub-serve learning.

Task-Based Functional Connectivity Strength Is Inversely Related to Learning

Behaviorally, the beneficial effects of motor sequence practice were assessed based on improved performance rate, which can be achieved by simple acceleration of single movements reflecting learning at the executive level, and greater tapping pattern consistency, which presumably reflects formation of internal sequence representation (100, 101). Here we show that these two complementary metrics to estimate learning are differentially associated with individual differences in FC strength between the two SMC and within the "active" SMC itself.

Particularly, participants who exhibited weaker FC between the two SMC showed greater improvement in performance rate. The effect within the "passive" SMC was localized to the hand knob, indicating that greater inter-hemispheric segregation between somatomotor units representing hand movements facilitated learning at the executive level. Such increased autonomy between the two somatomotor hand areas may reflect the release from inter-hemispheric inhibition—an effect postulated by transcranial magnetic stimulation (TMS) studies (102, 103). In fact, it has been shown that virtual "lesion" to the "passive" SMC induced by repetitive TMS leads to improved performance in the ipsilateral hand, presumably due to the suppressed inter-hemispheric inhibition (104–108). The inter-hemispheric inhibition is also reduced following unimanual training (109–111) and is associated with faster performance not only in the trained, but in the untrained hand as well (111). Alternatively, the improved performance associated with greater segregation between the two SMC reported here

may also indicate beneficial effects of release from irrelevant somatosensory input from the "passive" hemisphere. Indeed, the cluster showing significant effect within the "passive" SMC is located slightly posteriorly to the central sulcus encompassing the somatosensory hand area. To reliably dissociate between somatosensory and motor representations nested closely together around the hand knob, however, higher spatial resolution of the fMRI data is required. In any case, we suggest that the facilitatory effect of greater segregation between somatomotor representations is selective to the effector engaged in the task (i.e., the hand as compared to other body parts). Thus, effector-selective "pruning" of inter-hemispheric connections may facilitate learning primarily at the level of motor execution rather than movement synergy and sequence representation. It is worth noting, however, that under certain conditions, influences from the "passive" SMC are excitatory and may facilitate performance in a sequence-specific manner (48, 112).

In addition to a faster performance rate, which may develop due to more efficient execution of single movements regardless of their serial order, repeated experience with the motor sequence also shapes the tapping pattern of that sequence (76). Being determined by the relative spacing between the keypresses, this pattern may vary at the beginning, but stabilizes by the end of training (75). In the current study, participants who expressed a more stable performance by the end of training, hence generating a highly reproducible pattern when tapping the sequence, also exhibited weaker FC within the "active" SMC itself during the task. Animal studies suggest that same movements can be generated by various activity patterns within the motor cortex (64, 113). With repeated experience, however, the variability in these patterns decreases (64, 114). The greater reproducibility of the spatiotemporal patterns of neural activity concurs with the emergence of movement stereotypy and, therefore, may indicate the formation of dedicated internal representations of a new motor synergy. During initial phases of skill acquisition, these neural representations are shaped through selective activation of specialized neural populations and tuning of their firing rate (115). Evidence from fMRI studies on motor sequence learning in humans points out to similar processes (46, 47, 52). Our current results are thus consistent with the existence of an experience-driven mechanism of selective tuning and stabilization among neural populations representing the performing hand. We suggest that greater selectivity and stabilization of task-relevant representations are reflected in the reduced FC strength within the "active" SMC during the task.

Concurrently, the degree of task-based FC strength between the "active" SMC and SMA was also inversely related to the degree of performance consistency. Together with task-induced integration between these two regions, which was indicated by increases in FC strength during the task compared to the resting state, such relationship suggests that selective tuning at the lower level of primary somatomotor cortex may be governed by higher level processes within the SMA. The latter interpretation relies on three widely accepted views that are strongly supported by animal and human studies. First, the SMA has direct projections to the primary motor cortex (116). These projections are primarily excitatory (117) and are organized bilaterally with no clear lateralization (118). Second, the SMA is situated high within the hierarchy of the motor control system and is involved in initiation, monitoring and regulation of voluntary movements (119–122). Finally, this supra-motor region is crucially involved in sequencing of actions (123–125) and representations of practiced motor sequences (126–129). Accordingly, our results add up to accumulative fMRI evidence suggesting that SMA plays a role in encoding a sequence-specific pattern of finger movements (130) and orchestrates processes of rapid reorganization within the "active" SMC.

Methodological Considerations

Currently, there is a growing interest to study cognitive brain function using large-scale network modeling [for the recent reviews, please see (131, 132)]. This approach has been developed upon the foundations of graph theory by leveraging the mathematical description of a graph, which is composed of nodes and weighted edges, to represent brain networks. Nodes are commonly chosen as contiguous volumes/regions with boundaries defined either anatomically, using parcellation atlases, or functionally, using community detection algorithms. Edge weights are commonly defined by a degree of correlation or coherence between pairs of nodes. The sensitivity of this approach to dynamic changes within and between functional brain circuits depends on the size of each node, which consequently determines their overall number, and the way these nodes are grouped into networks. Whereas, both factors alleviate the multiple comparison problem, since they reduce high dimensionality of the whole-brain fMRI data, as a drawback, they also inherently reduce local specificity, thereby limiting special resolution of investigations to large-scale changes. For example, testing the integration of large-scale functional neural circuitry during the unimanual motor task, when participants practiced to generate different sequences upon visual guidance, Bassett et al. (41) provided evidence for growing autonomy between the visual and somatomotor systems over the course of a 6-week training (41). This segregation was also paralleled by disengagement of cognitive control networks including connections originated from frontal and anterior cingulate cortices. Whereas, such autonomy is consistent with the obvious decreased dependency on the visual cue and higher cognitive processes with practice [see also (36)], the researchers reported no significant changes in the overall degree of integration/segregation within the somatomotor network, which included primary somatosensory and motor regions representing both the active and passive hands, as well as SMA. However, when the analysis was conducted using the intra-network integration values calculated for each area separately, it revealed significant within-network changes that were associated with the amount of training [Supplementary Figure 8 in Bassett et al. (41)]. The results of the current study are consistent with this supplementary finding and further suggest that experience-driven reorganization within the somatomotor network occurs early in learning and involves both segregation and integration.

There are several key advantages of our study as compared to others in the literature. First, it is worth noting that our experimental design employed a motor sequence paradigm

without any external input or feedback during continuous periods of actual performance, thereby, minimizing influences of complex interactions among heterogeneous networks during the task state. The only external cue provided during the training was a change in color of the fixation cross, from red to green and from green to red, that indicated the beginning and the end of each training block, respectively. Second, this design also allowed us to separate the functional data collected during continuous performance periods (i.e., performance blocks) from the interleaved periods of rest. Finally, continuous nature of actual performance upon self-guided regime was advantageous for separation of FC measures from activation biases evoked at task transitions. In that way, FC values were calculated based on ongoing fluctuations of the fMRI signal during continuous periods of either resting or task state, thereby providing comparable estimates of connectivity patterns between those states.

CONCLUSION

Our results suggest that a hypothesis-driven seed-based FC approach reliably captures the task-induced changes in functional connectivity within the somatomotor network during the unimanual motor sequence task. These changes are not limited to the task-activated regions, hence revealing the existence of distributed processes of segregation and integration that act in parallel to allow for the generation of fine motor movements. These reconfigured connectivity patterns not only support task execution but also facilitate learning. The limited correspondence between the patterns of task-induced activity and connectivity is a known phenomenon within the scientific community. While there is an increasing recognition of potential benefits of combining the assessment of both metrics obtained from the task-based fMRI data series in order to understand cognitive brain functions (133), here we show that a careful consideration of the activation profile and functional specialization of each region of interest is not only desirable, but also critical to draw meaningful conclusions based on FC measures. In the current study, this approach, in combination with reliable behavioral correlates of motor sequence learning, allowed us to tease apart neural dynamics that may drive the adaptive processes during the initial phases of skill acquisition, the ones that need to be "silenced" and the ones that should be selectively pruned to rule out their task-irrelevant influences. Our results suggest that during the task, more segregated activity patterns between neural populations representing hand movements within the somatomotor cortex were beneficial for the development of both faster and more consistent performance by the end of training. Whereas, greater segregation between the two SMC may indicate effector-specific pruning of inter-hemispheric connections, which may facilitate gains at the level of motor execution, the same effect observed within the "active" SMC may possibly indicate the existence of selective tuning and stabilization processes, thereby resulting in more reproducible patterns of activity that allow to generate the motor sequence with greater consistency.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available because participants did not provide their explicit consent for public data sharing. Requests to access the datasets should be directed to JD, julien.doyon@mcgill.ca.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research ethics board of the RNQ (Regroupement Neuroimagerie Québec). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GA and JD designed the experiment. GA performed the experiment. EG analyzed the data. EG and JD wrote the original draft. GA and OL reviewed and edited the manuscript. OL provided expertise and feedback.

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Behavioral and Neuroanatomical Account of Impulsivity in Parkinson's Disease

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Impulse control disorder (ICD) is a major non-motor complication of Parkinson's disease (PD) with often devastating consequences for patients' quality of life. In this study, we aimed to characterize the phenotype of impulsivity in PD and its neuroanatomical correlates.

Methods: Thirty-seven PD patients (15 patients with ICD, 22 patients without ICD) and 36 healthy controls underwent a neuropsychological battery. The test battery consisted of anxiety and depression scales, self-report measures of impulsivity (Barratt scale and UPPS-P), behavioral measures of impulsive action (Go/No-Go task, Stop signal task) and impulsive choice (Delay discounting, Iowa gambling task), and measures of cognitive abilities (working memory, attention, executive function). Patients and controls underwent structural MRI scanning.

Results: Patients with ICD had significantly higher levels of self-reported impulsivity (Barratt scale and Lack of perseverance from UPPS-P) in comparison with healthy controls and non-impulsive PD patients, but they performed similarly in behavioral tasks, except for the Iowa gambling task. In this task, patients with ICD made significantly less risky decisions than patients without ICD and healthy controls. Patients without ICD did not differ from healthy controls in self-reported impulsivity or behavioral measurements. Both patient groups were more anxious and depressive than healthy controls. MRI scanning revealed structural differences in cortical areas related to impulse control in both patient groups. Patients without ICD had lower volumes and cortical thickness of bilateral inferior frontal gyrus. Patients with ICD had higher volumes of right caudal anterior cingulate and rostral middle frontal cortex.

Conclusions: Despite the presence of ICD as confirmed by both clinical follow-up and self-reported impulsivity scales and supported by structural differences in various neural nodes related to inhibitory control and reward processing, patients with ICD performed no worse than healthy controls in various behavioral tasks previously hypothesized as robust impulsivity measures. These results call for caution against impetuous interpretation of

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behavioral tests, since various factors may and will influence the ultimate outcomes, be it the lack of sensitivity in specific, limited ICD subtypes, excessive caution of ICD patients during testing due to previous negative experience rendering simplistic tasks insufficient, or other, as of now unknown aspects, calling for further research.

Keywords: impulse control disorder, Parkinson's disease, impulsive action, impulsive choice, structural MRI, Iowa gambling task, delay discounting task, stop signal task

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease characterized not only by motor symptoms as rigidity, hypokinesis, and tremor, but also by a variety of non-motor deficits. Among these non-motor symptoms, impulse control disorder (ICD) is the one that has a devastating effect on the quality of patients' life. In the population of PD patients, ICD manifests itself in a wide spectrum of impulsive behaviors such as pathological gambling, binge eating, hypersexuality, excessive shopping, and also repetitive excessive behaviors like punding (stereotyped purposeless repetitive behavior), hobbyism (internet use, reading, art work), walk-abouts (purposeless wandering), and hoarding (1, 2).

ICD in PD is usually believed to be a consequence of dopaminergic treatment (2, 3), but recent studies claim that there is an interaction of medication influence with underlying vulnerability to impulsive behavior (4, 5). Therefore, it is important to describe the behavioral pattern and neurobiological correlates of impulsivity in PD to track possible correlates of ICD in PD patients. Impulsivity is a heterogeneous concept, which can be understood as a personality trait or as a consequence of a neurobiological function deficit. Behavioral models of impulsivity distinguish impulsive action, which means inability to inhibit prepotent or unwanted actions (waiting impulsivity) or inability to stop ongoing action (stopping impulsivity), and impulsive choice, which includes aspects like high sensitivity to reward, risk taking, and preference of small immediate rewards to long-term gains (6). Impulsivity as a personality trait is measured by self-reported questionnaires, such as the Barratt scale or the UPPS-P scale; impulsivity as neurobiological deficit is measured by behavioral tasks.

Research using self-reported methods concluded that people with certain personality traits are in higher risk of developing ICD. Specifically, associations between ICD and higher novelty/sensation seeking, compulsivity, depression, and anxiety were found (3, 7–9). Impulsive personal traits have been previously associated with ICD in PD. Patients with ICD manifest elevated self-impulsivity in the Barratt scale (9, 10). Other risk factors for developing ICD in PD patients are younger age/younger age of disease onset, family history of behavior such as gambling or alcoholism, being man, and being single (2, 8, 11–14).

Previous research revealed increased impulsive choice, i.e., increased tendency to risky or disadvantageous decisions in general PD population (i.e., ICD status was not reported) (15–23) or in PD-ICD patients specifically (9, 24, 25). A tendency to irrational choices and early decisions in the Bead task, a test of reflection impulsivity, was observed in PD-ICD patients (26). These patients collected less information than PD patients without ICD or healthy controls before making a decision. However, results are not consistent. Study of Voon et al. (27) reported that PD-ICD patients have greater tendency to risk in comparison with patients without ICD, but only when there is only gain possibility, not in a situation with possibility of loss. Several studies did not find any differences in choice impulsivity between PD-ICD patients and healthy controls or PD patients without ICD (28–30) or in general PD population (31, 32). One study reported only statistical trend toward more risky decisions in the PD-ICD group in the Iowa gambling task (10). No significant differences in the performance between patients with and without ICD were reported in the Balloon Analog Risk Task (33–35). Ambivalent results were obtained regarding learning from the negative feedback. Several studies found lower sensitivity to negative feedback in PD-ICD (33, 36, 37), but others found no differences between ICD and patients without ICD or healthy controls (11, 35). Moreover, PD-ICD patients without medication showed decreased learning from negative feedback and increased learning from positive feedback compared to the PD-ICD patients on medication (11). Patients with ICD on dopamine agonists make faster decisions and more impulsive choices than patients off medication (28) and show enhanced sensitivity to risk (27).

Several studies reported increased stopping impulsivity (38–41) and waiting impulsivity (42) in the general PD population. However, there are also reports of intact impulsive action in PD patients without ICD (43) and in PD patients in general (ICD not specified) (44). Studies conducted on PD-ICD patients brought evidence of intact impulsive action (10, 45, 46); one study reported even faster Stop signal reaction time (SSRT), which means better ability to stop ongoing actions, i.e., lower stopping impulsivity in PD-ICD patients (43).

Structural imaging methods found evidence of cortical thickness abnormalities in PD-ICD in the structures related to impulse control and decision making, namely, the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), and corpus callosum (47–51). A gray-matter volume loss in amygdala and orbitofrontal cortex and volume changes in nucleus accumbens (NAcc) and in amygdala were observed in PD-ICD (21, 47, 48, 52).

There are only few studies directly comparing PD patients with and without ICD in impulsivity domains. Moreover, individual studies usually do not target multiple impulsive domains simultaneously, despite the heterogeneous nature of

impulsivity. The aim of our study was to describe the phenotype of impulsivity in PD patients with and without ICD by testing multiple impulsivity domains. We included three groups into our research: PD patients with ICD (PD-ICD), PD patients without ICD (PD-nonICD) and healthy controls (HC). We used self-reported impulsivity questionnaires (the UPPS-P and the Barratt scale), behavioral tasks for assessment of impulsive action (Go/No-Go task, Stop signal task), and impulsive choice (Iowa gambling task, Delay discounting task). We also measured depression, anxiety, and cognitive components influencing performance in impulsivity tasks (attention, working memory, and executive functioning). Moreover, structural magnetic resonance images (MRI) were obtained. We analyzed several brain regions, which were previously in the literature linked to impulsivity, inhibitory control, and decision making (**Table 3**).

Based on previous research, we hypothesized that PD patients with ICD, but not those without ICD, show greater impulsivity in self-reported scales. Further, we hypothesized that only PD-ICD patients show increased impulsivity in the Sensation seeking subscale of UPPS-P in comparison with healthy controls. We did not make any specific hypotheses for the other UPPS-P dimensions due to the lack of literature. We expect greater impulsive choice in the PD-ICD population, but intact impulsive action. No specific hypotheses were made about impulsive action and impulsive choice in patients without ICD due to conflicting literature and lack of literature targeting specifically PD patients without ICD. We expected PD-ICD patients to show brain structure abnormalities in comparison with healthy controls in the prefrontal cortex (orbitofrontal cortex, ACC, and DLPFC) and NAcc.

METHODS

Subjects

Thirty-seven patients with Parkinson's disease and 36 healthy controls took part in this study; the groups were matched by age, gender, education, and laterality. All patients were recruited from the University Hospital of St. Anne, Brno, Czech Republic. Healthy volunteers were recruited by advertising in local newspapers. Patients aged 25–75 with a diagnosis of Parkinson's disease based on the UK Brain Bank Criteria (53) were recruited in the study. All patients were under dopaminergic medication for at least 12 months preceding the examination and had stable doses at least for 4 weeks before testing. Exclusion criteria for all subjects were neurological or systemic disorder with effect on brain function (except PD in the patient groups), lesions in MRI scans, comorbid psychotic disease, affective disease or autism spectrum disorder, mental retardation, cognitive deficit (MMSE under 27), severe depression, and substance abuse.

Prior to the testing, data about age of the PD onset, Hoehn and Yahr stage, and medication calculated as levodopa equivalent dose were obtained, and cognition was examined using MMSE. Healthy volunteers were assessed by the Mini international neuropsychiatric interview [MINI; (54)] to exclude any subjects with psychiatric symptoms. The patients had no self-reported cognitive problems; none of them scored below 28 in Mini-Mental State Examination [MMSE; (55)]. Most of the patients were in stage 2 or 3 according to the Hoehn and Yahr Scale (56). Fifteen patients had ICD, and 22 patients were without ICD. Patients with ICD were selected by a neurologist based on interview with the patient and presence of ICD signs in their medical records. Only patients with severe behavioral problems connected to ICD were recruited. The patients showed the following ICD symptoms: gambling (5 patients), binge eating (3 patients), hypersexuality (2 patients), hobbyism (1 patient), compulsive buying (1 patient), hoarding (1 patient), punding (1 patient), pedantry (1 patient), and excessive cleaning (1 patient). Some of the patients showed more than one symptom of ICD. The study was approved by the Institutional Ethical Committee. All participants signed the informed consent prior to the beginning of the procedure. Characteristics of the sample are summarized in **Table 1**.

Experimental Procedure

Subjects underwent a neuropsychological battery of tests and questionnaires and performed four computerized behavioral tasks. The test battery included the Barratt scale (57) and the UPPS-P scale (58–60) for measuring self-reported impulsivity, the Montgomery-Asberg Depression Rating Scale (61), the Zung Self-Rating Anxiety Scale (62), and standardized measures of cognitive functions. Waiting impulsivity was measured by the Go/No-Go task (GNG), stopping impulsivity was measured by the Stop signal task (SST), and impulsive choice was assessed by the Delay discounting task (DDT) and the Iowa gambling task (IGT). Results are summarized in **Table 2**. Behavioral tests were created in E-Prime 2.0 software. The whole testing procedure took ∼2.5 h.

Impulsivity Questionnaires

We used the validated Czech translation of the Barratt scale for assessing impulsivity (57). This method includes aspects of non-planning impulsiveness, attentional impulsiveness, and motor impulsiveness. However, the three-factor structure has been questioned [e.g., (63, 64)]; therefore, only total score for this scale was calculated. Self-reported impulsivity was also measured by the Czech validated translation of the UPPS-P scale (58–60). The questionnaire consists of five subscales: Lack of premeditation (11 items), Lack of perseverance (10 items), Sensation seeking (12 items), Negative urgency (12 items), and Positive urgency (14 items), where urgency indicates the tendency to act impulsively under influence of emotions.

Behavioral Tasks

GNG Task

The GNG task contained two types of stimuli, the letter *A* was a Go stimulus and the letter *B* was a No-Go stimulus. Stimuli were in white color presented on the black screen. Subjects had to quickly react by pressing a key when letter *A* appeared and avoid the reaction when letter B appeared. A fixation cross preceded each stimulus. The whole task consisted of four blocks with 48 trials in each block. All subjects performed a short practice before the testing. The stimulus duration was 0.4 s; fixation cross duration varied from 1.1 to 2.6 s. Three parameters were analyzed from this task: No-Go commission errors percentage (percentage

TABLE 1 | Demographic, neurologic data and neuropsychological data of PD, PD-ICD and HC groups.

	PD-ICD ($n = 15$)	PD-nonICD ($n = 22$)	Healthy controls ($n = 36$)	Statistics value, p	Effect size
Gender M/F	11/4	10/12	19/17		
Age	59.27 (8.88)	69.18 (5.47)	66.14 (7.70)	$F_{(2, 70)} = 8.214$, $p = 0.001$	
Education	6.7, 13.3, 46.7, 33.4	4.5, 13.6, 68.2, 13.6	0, 16.7, 55.6, 27.7	$\chi^2_{(2)} = 0.658$, $p = 0.658$	
Socioeconomic status	6.7, 33.3, 46.7, 6.7	13.6, 22.7, 54.5, 9.0	2.8, 19.4, 52.8, 22.2	$\chi^2_{(2)} = 3.902$, $p = 0.142$	
Neurologic data					**d**
H a Y stage	2.53 (0.64)	2.48 (0.66)		$p = 0.799$, $t = 0.256$	$d = 0.085927$
Age of onset	50.80 (9.64)	62.55 (6.25)		$p < 0.001$, $t = -4.160$	$d = 1.445757$
Diseases duration	8.87 (4.17)	6.95 (4.63)		$p = 0.208$, $t = 1.282$	$d = 0.433676$
L-dopa equivalent dose	1289.75 (543.97)	1025.46 (567.18)		$p = 0.166$, $t = 1.414$	$d = 0.475602$
Neuropsychological data					η^2
MADRS	3.73 (5.68)	3.05 (3.84)	0.69 (1.83)	$F_{(2, 70)} = 5.202$, $p = 0.008$	$\eta^2 = 0.129$
SAS score	36.73 (5.40)	35.73 (5.25)	28.50 (6.59)	$F_{(2, 70)} = 14.980$, $p < 0.001$	$\eta^2 = 0.300$

Education (%), Primary, lower secondary, higher secondary, college.
Socioeconomic status (%), insufficient, unsatisfactory, satisfactory, very satisfactory.
MADRS, Montgomery Asberg Depression Rating Scale; SAS, Zung Self-reported Anxiety Scale; M, male; F, female.

of erroneous key press after No-Go trial), Go omission errors percentage (percentage of Go trials erroneously followed by no key press), and Go reaction time (average reaction time on correct Go trials). Go stimuli occurred in 83% and No-Go stimuli occurred in 17%; this ratio makes the task more cognitively demanding and the subjects prone to make more commission errors.

SST

Stimuli in the SST were white arrows pointing to the left or to the right; subjects had to press an arrow key pointing to the same direction as the arrow presented on the black screen. However, the subjects had to stop their reaction and press no key when the stimulus was followed by a visual stop signal (the arrow turned red). Stop signals appeared in 25% of trials. Delays in the presentation of stop signal (stop signal delay, SSD) varied during the task in order to prevent the subject from developing response pattern, the starting latency was 200 ms. When the subject succeeded in the trial, the latency increased by 45 ms; when the subject failed, the latency decreased by 45 ms. Each stimulus lasted until the subject reacted by pressing a key or for 1 s if there was no reaction from the subject. A fixation cross appeared before every stimulus; the duration of the cross was again variable between 1.1 and 2.6 s. The task consisted of four blocks with 48 trials in each block; a short practice preceded the testing procedure. The SSRT was calculated by subtracting the average SSD from the average Go reaction time. SSRT refers to the time that the subject needs to stop his/her reaction; the longer time needed, the more difficult it is to interrupt one's own actions; i.e., higher SSRT is linked with higher impulsivity.

DD

In the DD task, subjects were asked to choose between two possible rewards in every trial—a smaller but immediate reward or higher but delayed reward. For example, *Would you prefer to receive 510 CZK today or 990 CZK in a week?* There were five possible delays—1 day, 1 week, 1 month, 3 months, and 6 months—and two delayed reward levels 990 CZK (around 40 EUR) and 24900 CZK (around 980 EUR). These delays and rewards were set according to the pilot study. Questions with different combinations of delays and delayed rewards were presented in random order and the subject was asked if he or she prefers the immediate or the delayed reward. The amount of immediate reward varied in intervals of 20 CZK (in case of smaller delayed reward) or 500 CZK (in case of bigger delayed reward) until an indifference point, where the subjective value of the immediate reward is equal to the subjective value of the delayed reward, was found.

Two parameters were calculated for each delayed reward (k parameter and area under the curve). The hyperbolic discount parameter (k) was calculated by the equation $DR = I/(k^*D)$, where DR is delayed reward, I is immediate reward, and D is delay. Naturally, as the reward delay increases, the subjective value of this reward decreases (65). Larger values of k indicate steeper decline of the subjective value and therefore greater impulsivity. The second parameter was the area under the curve; the curve is estimated by the connection of indifference points for each delay reward. The lower the AUC means the steeper discounting and the higher impulsive choice (66).

IGT

The computerized version of IGT consisted of 200 trials (67, 68). In every trial, subjects had to make a series of choices between four card decks by pressing the key with number of the chosen deck. Two of the decks are disadvantageous (A and B) and two decks are advantageous (C and D). Subjects were informed that some of the decks were better than the other and they were instructed to play until the game ends and try to win as much money as possible. However, participants didn't know which decks are bad or good, how many trials had the game, or risk of losses in each deck. Impulsive behavior is associated with decks A and B. Deck A contains high immediate rewards with high risk of loss, and deck B contains high immediate rewards with low

TABLE 2 | Descriptive statistics of dependent variables and results of ANOVAs comparing PD-nonICD, PD-ICD, and HC groups.

	PD-ICD ($n = 15$)	PD-nonICD ($n = 22$)	Healthy controls ($n = 36$)	Statistic value, p	Effect size
Barrat scale	60.47 (7.54)	54.14 (5.60)	54.31 (6.48)	$F_{(2, 70)} = 5.537$, $p = 0.006$	$\eta^2 = 0.137$
UPPS-P PRE	20.60 (5.05)	19.77 (4.36)	18.67 (4.03)	$F_{(2, 70)} = 1.162$, $p = 0.319$	$\eta^2 = 0.032$
UPPS-P PER	20.33 (5.08)	19.14 (3.58)	16.83 (3.48)	$F_{(2, 70)} = 5.140$, $p = 0.008$	$\eta^2 = 0.128$
UPPS-P SS	22.07 (6.78)	23.64 (6.76)	26.25 (6.85)	$F_{(2, 70)} = 2.317$, $p = 0.106$	$\eta^2 = 0.062$
UPPS-P NU	27.27 (6.44)	25.18 (6.54)	25.51 (6.22)	$F_{(2, 69)} = 0.537$, $p = 0.587$	$\eta^2 = 0.015$
UPPS-P PU	28.33 (7.51)	28.27 (6.99)	26.69 (8.25)	$F_{(2, 70)} = 0.391$, $p = 0.678$	$\eta^2 = 0.011$
Go omissions %	18.95 (5.57)	18.76 (7,80)	16.94 (5.96)	$F_{(2, 70)} = 0.782$, $p = 0.461$	$\eta^2 = 0.022$
Go RT	419.36 (50.98)	418.03 (48.11)	402.83 (56.48)	$F_{(2, 70)} = 0.808$, $p = 0.450$	$\eta^2 = 0.023$
No-Go commissions %	18.65 (12.36)	25.97 (19.51)	22.45 (17.21)	$F_{(2, 70)} = 0.827$, $p = 0.442$	$\eta^2 = 0.023$
SSRT	298.46 (125.45)	242.36 (115.86)	281.97 (80.90)	$F_{(2, 69)} = 1.580$, $p = 0.213$	$\eta^2 = 0.044$
DD k 990	0.022 (0.046)	0.061 (0.125)	0.019 (0.050)	$F_{(2, 65)} = 1.886$, $p = 0.160$	$\eta^2 = 0.026$
DD k 24900	0.005 (0.0103)	0.077 (0.385)	0.004 (0.005)	$F_{(2, 69)} = 0.626$, $p = 0.538$	$\eta^2 = 0.018$
DD AUC 990	0.61 (0.31)	0.43 (0.29)	0.58 (0.34)	$F_{(2, 68)} = 1.854$, $p = 0.164$	$\eta^2 = 0.052$
DD AUC 24900	0.76 (0.25)	0.71 (0.23)	0.76 (0.30)	$F_{(2, 68)} = 0.251$, $p = 0.779$	$\eta^2 = 0.007$
IGT NET score 1st part	13.80 (29.33)	3.18 (25.80)	7.17 (25.28)	$F_{(2, 70)} = 0.729$, $p = 0.486$	$\eta^2 = 0.020$
IGT NET score 2nd part	39.07 (44.89)	−0.91 (33.84)	15.00 (37.43)	$F_{(2, 70)} = 4.925$, $p = 0.010$	$\eta^2 = 0.123$
IGT B % 1st part	24.55 (9.03)	32.55 (10.72)	31.00 (11.27)	$F_{(2, 70)} = 2.723$, $p = 0.073$	$\eta^2 = 0.072$
IGT B % 2nd part	16.86 (13.74)	36.64 (17.04)	30.58 (15.98)	$F_{(2, 69)} = 6.696$, $p = 0.002$	$\eta^2 = 0.163$
Digit span	14.47 (2.72)	14.18 (3.00)	14.67 (3.87)	$F_{(2, 68)} = 0.138$, $p = 0.872$	$\eta^2 = 0.004$
d2 speed	119.07 (24.99)	106.80 (24.50)	126.06 (19.99)	$F_{(2, 66)} = 4.624$, $p = 0.013$	$\eta^2 = 0.123$
d2 accuracy (error %)	9.25 (8.78)	8.67 (6.06)	9.39 (6.21)	$F_{(2, 66)} = 0.074$, $p = 0.929$	$\eta^2 = 0.002$
ToL moves	34.79 (17.08)	40.90 (24.29)	31.08 (19.67)	$F_{(2, 68)} = 1.493$, $p = 0.232$	$\eta^2 = 0.042$
ToL init. time	137.21 (71.74)	91.25 (42.32)	109.81 (55.98)	$F_{(2, 68)} = 2.841$, $p = 0.065$	$\eta^2 = 0.077$
ToL exec. time	337.71 (164.86)	360.10 (175.52)	278.33 (141.59)	$F_{(2, 68)} = 2.000$, $p = 0.143$	$\eta^2 = 0.056$

PRE, Lack of premeditation; PER, Lack of perseverance; SS, Sensation seeking; NU, Negative urgency; PU, positive urgency; Go RT, Go reaction time; SSRT, Stop signal reaction time; DD, delay discounting; AUC, Area under the curve; IGT, Iowa gambling task; IGT B %, percentage of B deck cards selections; ToL, Tower of London; moves, total number of moves made during the task; ToL inic. time; ToL exec. time.

risk of very high loss. IGT net score was calculated by subtraction of disadvantageous deck choices from advantageous deck choices [(C + D) − (A + B)]. We also compared the relative frequency of A and B deck choices.

Cognitive Abilities and Executive Functions

For working memory, the total score of Digit span subtest from WAIS-III (69) was analyzed. Three parameters from Tower of London (70) were calculated for assessment of executive functions—total move score, total initiation time, and total execution time. Attention was measured by test d2-R (71) with two analyzed parameters—speed (total number of processed items) and accuracy (percentage of omission and commission errors).

MRI Data Acquisition and Analysis

After the behavioral testing, the patients and controls underwent MRI scanning. Ten patients and eight controls did not undergo the acquisition due to MRI contraindications or inability to tolerate the procedure. The scanning was performed using a 3-T MRI scanner, SIEMENS MAGNETOM Prisma syngo (Siemens Medical Systems, Erlangen, Germany) at the Central European Institute of Technology of Masaryk University, Brno, Czech Republic. A high-resolution T1-weighted scan was acquired using the following parameters: MPRAGE sequence with repetition time = 2,300 ms, echo time = 2.34 ms, flip angle = 8°, voxel size 1.00 × 1.00 × 1.00 mm, matrix 240 × 224 × 224. Further three patients were excluded from the scanning because of excessive head movement resulting to significant motion artifacts not compatible with the automatic processing pipeline. The final size of the sample that competed MRI session was 16 PD-nonICD patients, 8 PD-ICD patients, and 28 healthy controls.

Volumetric segmentation was performed in this T1-weighted scan using the standard automated pipeline (72) implemented in the FreeSurfer image analysis suite, version 5.3.0 (http://surfer.nmr.mgh.harvard.edu/). The accuracy of the segmentation in each subject was visually inspected by a trained operator (P.F.). The volumes (adjusted for the estimated intracranial volume) and surface areas (in case of cortical regions) of several regions of interest (**Table 3**) and the volume of the whole brain, as provided by the automatic segmentation algorithm of FreeSurfer, were compared between the PD-nonICD, PD-ICD patients and healthy controls using one-way analysis of variance (ANOVA) with Bonferroni *post-hoc* multiple-comparison correction.

We performed statistical comparisons (two-sample *t*-tests) of subgroup of patients who underwent MRI scanning with the subgroup of patients who did not undergo MRI scanning to be

TABLE 3 | Anatomical regions of interest.

Anatomical region	Side
Caudate	R,L
Putamen	R,L
Nucleus accumbens	R,L
Accumbens area	R,L
Caudal anterior cingulate	R,L
Rostral anterior cingulate	R,L
Caudal middle frontal	R,L
Rostral middle frontal	R,L
Lateral orbitofrontal	R,L
Medial orbitofrontal	R,L
Pars orbitalis	R,L
Pars triangularis	R,L
Precentral gyrus	R,L
Insula	R,L

L, left; R, right.

sure that the MRI subgroup was not significantly different from the original patient group in the behavioral, demographic, and other measured parameters.

Statistical Analysis

Data were analyzed in IBM SPSS Statistics 24 software. We compared demographic characteristics, performance in computerized tasks, cognitive tasks, scores from questionnaires, and MRI parameters between groups of healthy controls, Parkinson patients with ICD, and Parkinson patients without ICD. The data from computerized behavioral tasks, questionnaires, and cognitive tasks were compared by one-way ANOVA without covariates. In cases of significant group differences, Tukey's *post-hoc* tests were applied. Sociodemographic characteristics (education, socioeconomic status) were analyzed by Kruskal–Wallis *H*-test; neurological data of the two patient groups were analyzed by independent *t*-tests. IGT net scores of the first and the second part of the task were analyzed in *jamovi* software by repeated measures ANOVA with Tukey's *post-hoc* tests with time (first vs. second part of the task) as within-subject factor and group as between-subject factor. Results are reported at $p < 0.05$ level of significance.

RESULTS

Demographic Data

The three groups did not differ in education or socioeconomic status (**Table 1**). The groups were also matched by age; the healthy controls were selected to have similar age to patients with 2 years tolerance. However, there was a difference in age between groups; patients with ICD were significantly younger than those without ICD and healthy controls (PD-nonICD vs. PD-ICD: $p < 0.001$, PD-ICD vs. HC: $p = 0.009$). The PD-ICD patients were younger than PD-nonICD patients at the time of the disease onset (PD-ICD vs. PD-nonICD: $p < 0.001$). There were no differences in disease duration, levodopa equivalent dose, or Hoehn and Yahr stage between clinical groups.

The group of patients who underwent MRI scanning did not differ from the group of patients without MRI in the cognitive abilities, behavioral parameters, or self-reported impulsivity. However, the groups significantly differed in age ($p = 0.028$, group with MRI mean = 67.56, $SD = 6.4$; group without MRI mean = 58.7, $SD = 10.5$).

Depression and Anxiety

There was a significant effect of group on scores of anxiety and depression. Both clinical groups (PD-ICD and PD-nonICD) had higher scores of depression than healthy controls (MADRS score PD-ICD vs. HC: $p = 0.018$, PD-nonICD vs. HC: $p = 0.043$). Both clinical groups also had significantly higher levels of anxiety than healthy controls (SAS score PD-ICD vs. HC: $p < 0.001$, PD-nonICD vs. HC: $p < 0.001$). No significant differences were detected between PD-nonICD and PD-ICD patients in anxiety or depression.

Impulsivity Questionnaires

There were significant group differences in the Barratt scale score. The PD-ICD group scored the highest on the Barratt scale, which means that PD-ICD patients were more impulsive than PD-nonICD patients ($p = 0.013$) and controls ($p = 0.008$). The PD-nonICD group and control group did not differ in the Barratt scale score ($p = 0.995$). In the UPPS-P scale, patients with ICD showed elevated score, as compared to healthy controls, in Lack of perseverance ($p = 0.017$). No differences between the groups were found in the other UPPS-P subscales. The PD-nonICD group did not differ from healthy controls in any of the self-reported impulsivity measurements and did not differ from PD-ICD except for the Barratt scale score.

Behavioral Tasks

There was no significant effect of group on performance in GNG, DDT, or SST (**Table 2**). Both groups of patients had similar RTs, accuracy, SSRT, and discounting parameters as healthy controls. Group differences were found in performance in IGT. Analysis revealed significant effects of time, group, and time vs. group interaction on the IGT net score [(C + D) − (A + B)]. There were no significant differences in the NET score in the first part of the task, but the PD-ICD group had significantly higher NET score than the PD-nonICD group ($p = 0.007$) in the second part of the task. No significant differences were found between healthy controls and PD-nonICD or between healthy controls and PD-ICD. There was significant effect of time vs. group interaction [$F_{(2, 70)} = 3.36$, $p = 0.041$]. *Post-hoc* tests revealed that only the PD-ICD group improved their NET score in the second half of the task; the difference was marginally significant in PD-ICD ($p = 0.055$) and not significant in other groups (HC: $p = 0.733$, PD-nonICD: $p = 0.993$). We further made analysis of particular deck selections in the first and second half of the task. There was a group difference in B deck preference in the second half of the task; specifically, the PD-ICD group selected cards from the B deck less likely than the PD-nonICD group (PD-ICD vs. PD-nonICD: $p = 0.002$) and healthy controls (PD-ICD vs. HC:

$p = 0.021$). No significant differences were found in A deck selection relative frequency.

Cognitive Abilities and Executive Functions

The three groups did not differ in working memory (Digit span). ANOVA revealed significant group differences in processing speed in d2 test. Patients without ICD were significantly slower than healthy controls (PD-nonICD vs. HC: $p = 0.009$). No significant differences were found between the PD-ICD patients and healthy controls or between the two patients' groups in the accuracy in d2 test. No significant differences were detected in total move score and total execution time in the Tower of London. However, we observed a trend in total initiation time between the PD-nonICD and PD-ICD group. The PD-ICD group showed longer incitation time than PD-nonICD group, but the comparison was only marginally significant (PD-nonICD vs. PD-ICD $p = 0.052$). All groups worked with similar accuracy in the test.

MRI

PD-nonICD patients differed from HC in the estimated intracranial volume (eICV) of the right nucleus accumbens area ($p = 0.002$), bilateral pars orbitalis ($p < 0.001$), the left pars triangularis ($p = 0.002$), and the left precentral gyrus ($p = 0.032$) (**Table 4**); PD-nonICD patients showed decrease of volumes in all of these regions (All presented *p*-values are Bonferroni-corrected for multiple comparisons.) PD-nonICD patients also showed cortical thinning of the left pars orbitalis ($p = 0.020$) in comparison with HC. PD-ICD patients in comparison with HC showed increase of the right caudal anterior cingulate area ($p = 0.003$) and right rostral middle frontal area ($p = 0.018$) and also increase of total volumes of these regions (right caudal ACC, $p = 0.010$, right rostral middle frontal $p = 0.007$). However, differences in eICV volumes in these areas did not reach significance in the case of PD-ICD group. Both groups—PD-nonICD and PD-ICD—showed a decrease in the eICV volume of the right precentral gyrus in comparison with HC, but none of the results reached significance in *post-hoc* testing ($p > 0.05$). In the comparison of PD-nonICD and PD-ICD, only total volumes of bilateral pars orbitalis (right $p = 0.029$, left $p = 0.039$) and right caudal anterior cingulate ($p = 0.041$) differed, with PD-ICD patients having greater volumes. Comparison of cortical areas, eICV volumes, or cortical thickness between the two patient groups did not bring any significant results.

TABLE 4 | Results of anatomical structures comparisons—significant contrasts.

Volumes	*p*	*F*	Significant contrasts
Right accumbens area	0.022	4.130	PD-nonICDxHC
lh pars orbitalis	0.013	4.737	PD-nonICDxHC, PD-nonICDXPD-ICD
rh caudal anterior cingulate	0.012	4.850	PD-nonICDXPD-ICD, PD-ICDxHC
rh pars orbitalis	0.005	5.841	PD-nonICDXPD-ICD, PD-nonICDxHC
rh rostral middle frontal	0.009	5.202	PD-ICDxHC
Volumes eICV			
Right accumbens area	0.003	6.688	PD-nonICDxHC
lh pars orbitalis	0.000	10.515	PD-nonICDxHC
lh pars triangularis	0.002	7.074	PD-nonICDxHC
lh precentral gyrus	0.013	4.718	PD-nonICDxHC
rh pars orbitalis	0.000	13.144	PD-nonICDxHC
rh precentral gyrus	0.021	4.160	No significant contrast
Thickness			
lh pars orbitalis	0.021	4.171	PD-nonICDxHC
Area			
rh caudal anterior cingulate	0.005	6.006	PD-ICDxHC
rh rostral middle frontal	0.022	4.146	PD-ICDxHC

Volumes eICV, estimated intracranial volume; lh, left hemisphere; rh, right hemisphere.

DISCUSSION

In the study, several possible factors associated with ICD were compared across the groups (anxiety, depression, age, age of onset, disease stage, and duration). Among these factors, only age of onset and age differed between the ICD and non-ICD group. Patients with ICD were younger and had lower age of disease onset than patients without ICD. Our results support previous research reporting association between PD-ICD and younger disease onset or younger age (2, 11–14).

Elevated self-reported impulsivity in the Barratt scale in PD-ICD in comparison with HC and PD-nonICD is consistent with previous research in this population (9, 10, 13, 73). In the UPPS-P scale, our results did not confirm our hypothesis regarding elevated Sensation seeking in PD-ICD. The absence of differences in Sensation seeking in PD-ICD might be surprising, when some other studies found associations of higher Sensation/Novelty seeking with ICD in this population (7–9, 13) [but see Evans et al. (12)]. The differences might be due to using various measurement tools with different concepts of Sensation seeking. Regarding the UPPS-P dimensions, we found only one study that targeted these dimensions in PD-ICD (7). This work reported increased impulsivity in Lack of premeditation, Urgency, and Sensation seeking in PD-ICD in contrast with HC and elevated Sensation seeking in contrast with PD-nonICD patients. However, only the shortened 16-item UPPS scale was used and the scale was answered by close relatives of the patients not the patients themselves, which may cause inconsistency of their results with our findings. PD-ICD patients in contrast with HC showed elevated score only in the Lack of perseverance. Perseverance is defined as "the ability to remain focused on a task that may be boring and/or difficult." Lack of perseverance has been associated with poor resistance to distraction, harm avoidance, poor concentration on boring or difficult tasks, lower responsibility perception, and difficulties in dealing with frustration (74). Lower perseverance was reported in people with obsessive–compulsive symptoms, compulsive buying (74–77), bulimia (78), and self-injury behavior (79). One study found lower perseverance in PD patients with and without ICD (7). PD-ICD patients in our sample did not manifest higher levels of Urgency, which represents the aspect of emotional impulsivity. Taken together with no impairments in impulsive choice, it seems

that impulsivity in PD-ICD is not elevated by strong emotions unlike, for example, borderline disorder, where impulsivity is more prominent in intense emotional state (6, 80, 81). PD-ICD patients are more likely to avoid harm and lower their effort in boring or difficult situations. They have impaired ability to maintain long-term goal and facing the obstacles; when facing difficulties, they rather abandon the goal. Even though UPPS-P questionnaire is the most up-to-date personality model of impulsivity, it is not used in studies conducted on PD-ICD populations. Future research with larger sample sizes studying PD-ICD in the context of UPPS-P impulsivity model would be beneficial.

In accordance with our hypothesis, PD-ICD patients in our study did not show impairments in impulsive action (waiting and stopping impulsivity). Results were also negative for the non-impulsive group. Previous studies of impulsive action in general PD population brought mixed results (38–44). There might be several factors responsive for the inconsistency in impulsive action among studies. Differences in results can be caused by cognitive impairments in patients' groups, heterogeneity in the patients' samples, and by differences in task designs. Patients in studies have different clinical characteristics such as different disease stage and duration, cognitive impairments, and different severity of anxiety and depression. Some of the studies included patients with cognitive impairments and elevated depression in their samples (38, 45). Presence of cognitive deficits and depression were linked to lower efficacy of inhibitory performance in impulsive action tasks (38, 82). Further, patients with older age and later disease stages have greater difficulties when inhibiting their responses (38). Thus, it is possible that increased impulsive action observed in some studies in the previous literature might have been influenced more by impaired cognitive functioning or psychomotor slowing associated with markedly increased depression, rather than with increased impulsivity itself.

We expected elevated choice impulsivity in PD-ICD in comparison with healthy controls, but our results did not support this expectation. None of the clinical groups differed from healthy controls on Delay discounting. Unimpaired performance of PD-ICD patients on Delay discounting is in contrast with two studies (9, 24), which found elevated discounting in PD patients with ICD in comparison with HC and non-impulsive PD patients. However, PD-ICD patients in these studies had either lower IQ or working memory deficits or were more depressed than non-impulsive patients. All of these factors were previously associated with greater discounting (83–86). Consistently with our findings, another study (28) reported similar delay discounting comparing PD-ICD and HC. The results of DD studies in PD-ICD population remain inconsistent. It is again possible that presence of cognitive impairments or elevated depression could influence performance in this task in previous studies. Future research should focus on relationship of depression, cognitive deficits, and behavioral measures of impulsivity in this population.

In the IGT in our study, patients with ICD performed surprisingly the best from all groups. PD-ICD as the only group improved their performance in the second part of the task and made significantly less risky choices. PD-ICD patients differed from PD-nonICD and HC in B deck card preference. B deck is a deck with low frequent but very high losses and high frequent gains. This deck is disadvantageous in long-term outcome. Therefore, according to the basic IGT assumption, the frequency of B deck choice declines during the task in a healthy population (67). This basic IGT assumption is being questioned, since the high preference of B deck choices observed in a healthy population in many studies suggests that it is rather the gain–loss frequency than the long-term outcome that influences decision-making in IGT in a healthy population (87). Our results suggest that PD-ICD patients, unlike HC and patients without ICD, are less sensitive to gain-loss frequency and more sensitive to high punishments. Previous studies brought evidence of impaired IGT performance in PD patients (ICD not specified) (16–23, 88) and in pathological gamblers with Parkinson (25). The difference between our study and that of Rossi et al. (25) is that we also included other forms of ICD beside pathological gambling. We recruited some patients with gambling history into our sample. It is possible that these patients with gambling history were more aware of potential risk because of their previous problems and they already developed some strategies, which helped them during the task. In contrast with previous studies, we used a prolonged protocol consisting of 200 trials. The differences between groups were more prominent in the second part of the tasks where PD-ICD patients chose the cards from the disadvantageous deck less frequently than in the first part. It seems that this prolonged version is more sensitive to describe learning from the consequences of the traditional 100 card version. We further analyzed not only the NET score but also the preference of particular packages. This four-deck approach seems to be useful, because it provides more information about decision strategies of participants.

Having in mind the age differences between groups of patients in our study, the role of age in the context of IGT results should be considered. PD-ICD in our study performed better than PD-nonICD, and they were also younger than PD-nonICD patients. Biars et al. (29) reported that increasing age negatively influenced IGT performance. Some studies found older adults to have greater tendency to less advantageous decisions in IGT than younger adults (89, 90). It is possible that older adults use different cognitive strategies and are not able to learn from the feedback as effectively as younger adults (89). On the other hand, studies reporting impaired performance in the PD or PD-ICD group in IGT found no significant age differences between compared groups (16, 18, 20–22, 25). Further investigation in this field would be beneficial.

As for cognitive functions, patients did not show any significant impairments except slower processing speed in the d2 test in PD non-ICD in contrast with HC. It may be surprising, because a decline of cognitive functions is linked to PD and cognitive impairment was previously find in patients with ICD (5). However, only patients with high MMSE scores were recruited, and therefore, those with potential cognitive problems were excluded from the testing. The slower processing speed of PD-nonICD patients in contrast to HC in d2 can be attributed to age, because the PD-nonICD group was the oldest one. Slower

processing speed can also indicate attentional problems. It is possible that PD-nonICD patients are able to complete the task with similar accuracy as other experimental groups, but it costs them more effort; as a result, they need more time to process the same amount of items.

Although there were no impairments in PD-ICD on behavioral tasks, MRI scanning revealed structural differences between the three groups in the structures involved in inhibitory control and decision making. PD-ICD patients showed volume increase of ACC in comparison to PD patients and healthy controls. Our results correspond with previous research, which found increased thickness of ACC cortex in PD-ICD (48, 49, 51). Decreased functional connectivity of ACC with nucleus accumbens was previously associated with impulsive–compulsive behavior in PD (51). ACC is an important component of the reward system. It is involved in subjective evaluation of immediate and delayed rewards in delay discounting (91). Some researchers suggest that this structure is also important for conflict monitoring in situations with low predictability and high error rate; when the subject is required to adjust behavior after error response, it is needed for learning from the negative feedback (49, 92). Considering an increase in ACC volume together with the improvements in PD-ICD group during the second part of the IGT task, it suggests that PD-ICD patients were the most sensitive to the negative feedback. PD-ICD patients in our study showed an increase of volume and area in the right rostral middle frontal region in comparison with HC. Middle frontal region abnormalities in PD-ICD population were previously reported Biundo et al. (47) and Yoo et al. (50), who observed cortical thinning in PD-ICD. Increased activity of the right middle frontal gyrus was previously observed during impulsive action tasks (93). This region is associated with working memory, norm- or rule-related behavior, and making strategic decisions in social context (94, 95).

However, our results are not entirely consistent with previous research. One study of PD-ICD patients reported no structural differences between PD-ICD and PD-nonICD or HC (96). Recent research brought also evidence of structural differences in orbitofrontal cortex and nucleus accumbens in PD-ICD (47–49), but our group comparisons were negative regarding these regions. Differences in anatomical findings across the studies might be caused by different analysis approaches and further by the presence of cognitive impaired individuals in some of the studies, as well as by variability of ICD patients in behavioral manifestations of ICD, in disease duration and disease progression. Disease progression and symptom severity are very important factors. For example, PD-ICD patients in the study of Pellicano et al. (48), which observed more extensive structural changes than our study, were in more advanced stage and showed more severe disease symptoms than non-impulsive patients. On the other hand, the study of Ricciardi et al. (96), which did not find any structural differences, included patients in earlier stage of the disease and with shorter disease duration than our study. Some studies tested patients with mild cognitive impairment (47, 49). Most of the studies included patients with variable ICD symptoms often with more than one manifestation of ICD. We also included variable ICD sample into our study. It is possible that particular subtypes of impulsive behavior like gambling, hypersexuality, or binge eating differ from each other in behavioral impulsivity or in their neurobiological correlates.

Patients without ICD differed from healthy controls in the regions of inferior frontal gyrus, right nucleus accumbens, and left precentral gyrus. These findings also indicate that patients without ICD have some brain pathology in regions relevant for impulsivity. This corresponds with previous MRI research conducted on the general PD population (42, 97–100).

This study has several limitations. First of all, the research sample consisted of a small number of patients due to the inclusion of only patients with severe impulsive problems and avoiding patients with cognitive deficit. Even though the prevalence of ICD in the population is higher, we decided to include only patients with severe ICD, which has a truly observable effect on their day-to-day life (e.g., substantial financial losses due to gambling). We deliberately decided to exclude patients with subclinical or borderline behavioral problems, because PD patients often manifest with a variety of behavioral problems, but only problems that differ from premorbid level of everyday functioning should be considered as a disorder. Hence, the inclusion of borderline patients would affect the validity of the study.

Secondly there is heterogeneity in our patient sample—we included patients with various manifestations of ICD. Future research studies could separately analyze individual subtypes of PD-ICD. Another limitation is the age difference between the PD-ICD and PD non-ICD patients. This factor needs to be considered, and caution should be exercised in interpretation of group differences. Moreover, not all of our patients were able to successfully undergo MRI testing; therefore, the sample for MRI testing was smaller than the sample for behavioral testing. However, the statistical comparison did not find any differences in self-reported impulsivity and behavioral performance between the subgroup of patients who underwent the MRI assessment and the group of patients without MRI testing. The last factor that may have influenced the results was the presence of some patients with a history of ICD. It is possible that previous personal experience could influence the behavior of these patients during the testing.

CONCLUSION

The discrepancy between the presence of florid ICD signs, both in clinical follow-up and in self-reported impulsivity scales, and the comparable or even better performance of PD-ICD patients in rather well-established behavioral tasks is rather intriguing. This stalemate is further accentuated by significant structural differences in various neural nodes related to inhibitory control and reward processing in PD-ICD patients. Be it the lack of sensitivity in specific, limited ICD subtypes, excessive caution of ICD patients due to previous negative experience rendering simplistic tasks insufficient, or other, as of now unknown aspects, the issue of impulsivity in PD definitely warrants further research, ultimately to allow proactive prevention of this debilitating complication of PD.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Etická komise Masarykovy univerzity. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PH, PF, PL, MS, MBal, MBar, and TK participated in designing the project and defining the aims and hypotheses. PF, RŠ, MBal, and MBar were responsible for patient recruitment and neurological examinations. PH and PL performed neuropsychological testing. PH and PF performed the data analysis and wrote the manuscript draft. All co-authors provided their comments to the manuscript draft.

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Cerebellar Contribution to Motor and Non-motor Functions in Parkinson's Disease: A Meta-Analysis of fMRI Findings

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Background: Parkinson's disease (PD) results in both motor and non-motor symptoms. Traditionally, the underlying mechanism of PD has been linked to neurodegeneration of the basal ganglia. Yet it does not adequately account for the non-motor symptoms of the disease, suggesting that other brain regions may be involved. One such region is the cerebellum, which is known to be involved, together with the basal ganglia, in both motor and non-motor functions. Many studies have found the cerebellum to be hyperactive in PD patients, a finding that is seldom discussed in detail, and warrants further examination. The current study thus aims to examine quantitively the current literature on the cerebellar involvement in both motor and non-motor functioning in PD.

Methods: A meta-analysis of functional neuroimaging literature was conducted with Seed-based D mapping. Only the studies testing functional activation in response to motor and non-motor paradigms in PD and healthy controls (HC) were included in the meta-analysis. Separate analyses were conducted by including only studies with non-motor paradigms, as well as meta-regressions with UPDRS III scores and disease duration.

Results: A total of 57 studies with both motor and non-motor paradigms fulfilled our inclusion criteria and were included in the meta-analysis, which revealed hyperactivity in Crus I–II and vermal III in PD patients compared to HC. An analysis including only studies with cognitive paradigms revealed a cluster of increased activity in PD patients encompassing lobule VIIB and VIII. Another meta-analysis including the only 20 studies that employed motor paradigms did not reveal any significant group differences. However, a descriptive analysis of these studies revealed that 60% of them reported cerebellar hyperactivations in PD and included motor paradigm with significant cognitive task demands, as opposed to 40% presenting the opposite pattern and using mainly force grip tasks. The meta-regression with UPDRS III scores found a negative association between motor scores and activation in lobule VI and vermal VII–VIII. No correlation was found with disease duration.

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Discussion: The present findings suggest that one of the main cerebellar implications in PD is linked to cognitive functioning. The negative association between UPDRS scores and activation in regions implicated in motor functioning indicate that there is less involvement of these areas as the disease severity increases. In contrast, the lack of correlation with disease duration seems to indicate that the cerebellar activity may be a compensatory mechanism to the dysfunctional basal ganglia, where certain sub-regions of the cerebellum are employed to cope with motor demands. Yet future longitudinal studies are needed to fully address this possibility.

Keywords: Parkinson's disease, fMRI, motor, cognition, symptoms, meta-analysis

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative movement disorder characterized by classic symptoms including tremor, bradykinesia, rigidity, akinesia, postural instability, and balance problems. Its diagnosis is mainly made through the careful assessment of these symptoms, which become the target of subsequent treatment interventions. However, non-motor functions comprising cognitive, sensory, sleep, emotional, and social abilities are also affected by the disease [for a review, see (1–3)] and may even precede the appearance of the motor symptoms (4). Furthermore, even though the non-motor symptoms can be more detrimental to patients' quality of life than the motor signs (5), they have not yet received the same amount of attention in clinical and research settings alike.

A plethora of studies have established that the neurological underpinnings of PD are tied to the neurodegeneration of the basal ganglia, more specifically the dopaminergic cells of the substantia nigra *pars compacta*. The traditional model of PD states that such a dopaminergic denervation leads to hyperactivity in basal ganglia output nuclei (globus pallidus *internus* and substantia nigra, *pars reticulata*), hence resulting in increased inhibition from thalamocortical and brain stem motor regions, which subsequently leads to impaired movements (6, 7). Indeed, several models have been proposed that discuss how basal ganglia dysfunction has cascading effects on interconnected circuits, including the thalamus and cortical (motor) regions that result in some of the characteristic motor symptoms seen in PD [for an overview, see (8)]. Yet, whether these effects indicate the spreading of the underlying pathology into the non-affected areas, or an adaptive/compensatory response to the basal ganglia neurodegeneration is largely unknown.

Furthermore, although basal ganglia dysfunction can explain many of the motor symptoms seen in PD, it does not adequately explain the non-motor symptoms of the disease, hence suggesting that other brain structures, and the cerebellum in particular, may also be involved in the pathophysiological process. In fact, several lines of evidence support this notion. First, certain PD motor symptoms, like tremor, have been linked to abnormal functional connectivity between the basal ganglia and the cerebellum, via the thalamus (9, 10). Second, despite the fact that the cerebellum has traditionally been considered to play a merely supporting role in motor functioning, adjusting and fine-tuning movements based upon an internal model (11) as well as through a feedforward system (12), it has recently been suggested that the cerebellum is involved in monitoring performance for several types of behaviors (13). To this effect, early cerebellar lesion and neuroimaging studies have linked the cerebellum to a wide range of higher cognitive functions, such as working memory, executive functioning, planning, set shifting and more (14, 15). These findings have been further confirmed and expanded through reports that the cerebellum also plays a role in pain, mood disorders and emotional processing, sensorimotor integration, as well as language and learning (16–20). Finally, investigations in healthy individuals have revealed that the basal ganglia and cerebellum are working synergistically to produce efficient motor and non-motor functioning (19). For instance, both sub-cortical structures are implicated in reinforcement learning and reward (18, 21), motor planning and action understanding (22, 23), as well as sensorimotor prediction and control (24, 25) amongst others. Thus, together these findings likely suggest that the cerebellum is instrumental in non-motor symptoms in PD. Indeed, a recent meta-analysis on volumetric cerebellar changes in neurodegenerative disorders proposed that the cerebellum plays a bigger role in cognitive, than in motor symptoms experienced by PD patients (26). Neuroimaging studies have also been consistent with this notion, as positron emission tomography studies using ^{18}F-fluorodesoxyglucose have reported increased metabolism in the cerebellum to be linked to cognitive impairment in PD patients, hence characterizing the observed cerebellar hypermetabolism as a part of a "PD related cognitive pattern" (27–30) that is not modulated by treatment interventions (27). There are also increasing amounts of evidence from functional magnetic resonance imaging (fMRI) studies, which support the notion of aberrant activity in the cerebellum of PD patients during both task and rest conditions (31–35).

Despite the recent advances described above, however, there are several important factors that limit our understanding of the role of cerebellum in PD. First, in most imaging studies with PD patients, the cerebellum is commonly reported to be active in response to non-motor paradigms; yet its activation is rarely discussed in detail or seldom constitutes the focus of the study. Moreover, even though anatomical boundaries of cerebellar regions have been clearly defined with specialized functional topography (36, 37) and atlases are readily available (38, 39), the findings are commonly described in the context of the cerebellum as a whole, without reference to its sub-regions. It

is therefore not clear whether certain parts of the cerebellum are more implicated than others in relation to motor and non-motor functioning in PD. Finally, the potential role of the cerebellum in PD has been discussed elsewhere in narrative reviews (40, 41), but the cerebellar involvement remains largely unclear, especially in regards to the pathological and/or compensatory mechanisms at play. With exception of one meta-analysis of cerebellar gray matter atrophy across several neurodegenerative conditions (that did not report any findings in PD patients) (26), the existing literature lacks a quantitative and systematic review of cerebellar findings in PD based upon functional neuroimaging methods. In response to this knowledge gap, the current systematic review and meta-analysis appraises the fMRI literature on cerebellar involvement in both motor and non-motor processes in patients with PD. First, a general analysis including all fMRI studies comparing task-related activity in PD vs. matched control participants is carried out, before stratification of motor and non-motor studies, which are then examined separately in order to determine whether certain regions of the cerebellum are specifically implicated in these functions. Relationships with disease severity and duration are also assessed. With this, we aim to develop a greater insight into the role of the cerebellum in PD, with a particular focus on its involvement in motor and non-motor functioning.

METHODS

Study Eligibility and Research Methods

An extensive search was carried out on Pubmed, and included the following search terms:

- "Parkinson's Disease" [AND] "functional magnetic resonance imaging" [AND] cerebellum
- "Parkinson's Disease" [AND] "fmri" [AND] cerebellum
- "Parkinson's Disease" [AND] "fmri"
- "Parkinson's Disease" [AND] "functional magnetic resonance imaging".

We then used the following inclusion criteria for the selection of eligible studies. They had to: (1) be published in peer-reviewed journals, written in English and not behind paywalls that were not covered by McGill University Library subscriptions; (2) include a healthy control group that was compared with PD patients; (3) assess functional brain activity with fMRI in response to a task paradigm; and (4) include results from original research, not from secondary sources (i.e., reviews). The meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (see **Figure 1** for overview, and **Supplementary Materials** for the PRISMA checklist). The last search was conducted on December 9th, 2019.

Meta-Analysis

Cerebellar activation coordinates and the effect size from comparisons between PD and a control group in response to motor or cognitive paradigms were first extracted from each paper, together with scanning and preprocessing parameters. The meta-analysis was carried out using seed-based mapping (SDM) [(42), https://www.sdmproject.com], a software that conducts meta-analyses similarly to the activation likelihood estimation, and multilevel kernel density analysis approaches, but with integrated sensitivity analyses, effect size estimation, as well as the option to include negative and nil-findings. Data were then preprocessed to achieve a voxelwise recreation of the studies using an isotropic Full Width Half Maximum (FWHM) of 20 mm, and a voxel size of 2 mm^3. Third, the global means of all studies were analyzed (the meta-analysis) using 50 imputations, creating beta-coefficients and a mean activation map including the associated variance. Finally, the maps were corrected for multiple comparisons with Family Wise Error (FWE) using 500 permutations. However, as corrected maps were not sensitive enough to detect clusters associated with group differences, an uncorrected $p > 0.005$ with an extent threshold of >10 voxels was later used for the meta-analyses.

Data preprocessing included information on coordinates space (MNI or Talairach) and on the analysis package used (SPM, FSL or "other"). Each study's t-threshold was included in the analyses as a measure of the statistical threshold used for the findings reported in each study. In cases where this was not stated in the paper, SDM's built-in effect-size estimation tool was used to provide effect-size threshold estimates. Information on subjects' age, gender ratio, as well as information on the patients' UPDRS III, Hoehn & Yahr scores and disease duration was extracted from the papers whenever available (see **Table 1**). The disease duration and UPDRS scores were later used for correlation analyses in the meta-analysis.

One of the benefits of our method (SDM, described above) is the option to include studies with nil-findings. These studies were included in the main analysis as studies with no peaks, allowing us to increase accuracy of our analysis. In studies where neither Z-scores, nor F-values were reported in the between groups comparisons, the SDM's conversion tool was utilized to obtain the corresponding t-statistic. As the effect size was not given in a few of the articles, the peaks were then marked as "positive" or "negative," hence denoting direction of the contrast used. Because of the variability in study methodologies, and to include as much data points as possible, studies utilizing an ROI approach were also included in the analysis, even though in literature, the cerebellum may be an uncommon ROI.

The findings were then inspected for heterogeneity and bias by examining the peak values and the corresponding I^2 statistic and its funnel plot. I^2 is a test of heterogeneity for meta-analytical studies, where a low value generally represents a low level of heterogeneity. Egger statistics were also examined by plotting the effect size against precision of the studies as a measure of publication bias. Finally, the SDM toolbox provided results in MNI coordinate space which were confirmed both with the Diedrichsen probabilistic cerebellar atlas (39) in FSL Eyes (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLeyes), as well as with Schmahmann et al.'s MRI cerebellum atlas (38).

Medication Status

To be as inclusive as possible, studies that included patients who were not asked to refrain from taking medication (i.e., in an ON-state) were also included. Since previous studies have found

TABLE 1 | Study demographics of all included studies.

References	PD (n)	HC (n)	f/m PD	f/m HC	PD age (±SD)	HC age (±SD)	UPDRS III	Hoehn & Yahr	Disease duration (years)	Nil-finding	Task
Vriend et al. (43)	21	37	4/10	8/6	59.0 (±10.4)	56.2 (±9.9)	21.6 (±8.3)	1.9 (±0.4)	0.19 (±0.31)	No	Cognitive control task
Filip et al. (44)	21	28	10/11	14/14	68 (±4.85)	66.4 (±6.9)	Not stated	2.24 (±0.57)	7.69 (±3.8)	No	Cognitive: impulse control
Heller et al. (45)	26	25	1/11	5/7	63.9 (±8.4)	62.6 (±9.0)	26.8 (±11.6)	2	8.18 (±6.83)	No	Emotional processing
Yu et al. (31)	8	8	6/14	10/10	59.4 (±8.4)	59.5 (±9.5)	31.1 (±10.8)	Not stated	5.9 (±2.6)	No	Motor and auditory task
Martin et al. (46)	22	22	4/10	5/9	52.5 (±10.7)	48.5 (±12.4)	15.6 (±6.4)	1.4 (±0.6)	Not stated	No	Motor and planning task
Burciu et al. (47)	20	20	1/8	5/10	65.8 (±8.0)	64.8 (±8.8)	31.9 (±9.6)	2.0 (±0.3)	4.14 (±1.65)	No	Motor and visual
Rottschy et al. (48)	23	23	8/14	8/14	67.2 (±6.2)	65 (±4.4)	23.9 (±16.1)	1.5 (±0.9) (ON)	4.7 (±4.2)	No	Motor and working memory task
Pinto et al. (49)	9	15	7/13	5/5	59 (±9)	55 (±11)	33 (±13)	Not stated	14 (±7)	No	Motor hand movement and speech
Caproni et al. (50)	11	11	3/8	3/8	65 (±4.98)	65.1 (±5.86)	20 (±4.5)	2	3.8 (±1.5)	No	Motor task
Husárová et al. (51)	20	21	9/11	10/11	55.4 (±9)	57 (±7.3)	18.08 (±3.8)	Not stated	2.5	No	Motor task
Poisson et al. (52)	6	10	2/4	6/4	65 (±10)	53.6 (±8.5)	16 (±5.1)	Not stated	5.4 (±4.6)	No	Motor task
Wu and Hallet (33)	12	14	4/8	4/8	61.2 (±7.64)	61.8 (±no SD)	25.5 (±7.4)	2.04 (±0.62)	6.33 (±2.84)	No	Motor task
Jia et al. (53)	22	22	8/14	8/14	61.04 (±4.38)	60.59 (±4.64)	16.45 (±4.63)	1.64 (±0.44)	4.04 (±1.81)	No	Motor task
Toxopeus et al. (54)	12	18	5/7	9/9	59 (±9)	58.7 (±5.4)	22 (±7)	2.0 (±0.5)	6 (±4)	No	Motor task
Planetta et al. (55)	14	14	7/12	17/5	64 (±8.7)	61.9 (±8.4)	29.6 (±5.3)	Not stated	5.9 (±5.5)	No	Motor task
Neely et al. (56)	14	14	5/5	6/5	64.0 (±8.7)	60.2 (±9.2)	29.6 (±5.3)	Not stated	Not stated	No	Motor task
Cerasa et al. (57)	10	11	8/12	10/10	64.2 (±13.6)	63.4 (±9.3)	27.5 (±8.8)	2.5 (±0.6)	7.2 (±3.5)	No	Motor task
Schwingenschuh et al. (58)	20	10	5/7	9/9	66.8 (±7.2)	33.9 (±8.9)	37.9 (±11.1)	2.2 (±0.4)	6.3 (±3.1)	No	Motor task
Kraft et al. (59)	12	12	5/10	5/10	60.8 (±7.3)	53.0 (±12.0)	21.0 (±3.3)	1.8 (±0.5)	3.1 (±1.1)	No	Motor task
van der Stouwe et al. (60)	12	18	7/9	8/7	59 (±9)	59 (±5)	21.5 (±6.9)	1.9 (±0.5)	Not stated	No	Motor task
Wu et al. (61)	15	15	Not stated	Not stated	59.73 (±8.27)	60.3	20.67 (±3.48)	1.7 (±0.37)	3.47 (±1.6)	No	Motor task
Wurster et al. (62)	10	10	7/14	7/12	66.4 (±7.2)	64.9 (±8.14)	20.7 (±9.1)	2 (±0.83)	6 (±5.6)	No	Motor task
Hughes et al. (63)	16	15	11/10	11/11	63.9 (±7.5)	66.5 (±5.9)	31.3 (±11.)	2.0 (±0.5) (ON)	7.6 (±3.7)	No	Motor task
Lemos et al. (64)	19	22	6/15	16/21	64.9 (±6.3)	66.4 (±9.5)	Median: 19 (±19)	Median: 1.5 (±1)	4 (±8)	No	Saccade task
Takeda et al. (65)	9	7	5/4	5/2	54	51	Not stated	2.2	Not stated	No	Sensory: olfactory
Tessitore et al. (66)	20	18	9/11	8/10	60 (±8.9)	55.9 (±5.2)	10.1 (±7)	1.4 (±0.5)	1.2 (±0.5)	No	Sensory: pain
Harrington et al. (67)	21	19	7/5	5/7	67 (±9.4)	64.6 (±8.5)	29.6 (±10.4)	2	Not stated	No	Working memory task
Snijders et al. (68)	24	21	3/9	6/10	60.2 (±8.9)	57.0 (±9.1)	31.6	Not stated	8.45	Yes	(Imagined) motor task
Maidan et al. (69)	20	20	8/16	4/6	72.9 (±1.6)	69.7 (±1.3)	29.8 (±2.4)	Not stated	6.8 (±1.3)	Yes	(Imagined) motor task
Baglio et al. (70)	15	11	4/11	7/4	66.5 (±6.4)	66.9 (±5.7)	21.5 (±7.24)	1.56 (±0.46)	Not stated	Yes	Cognitive: attention and inhibition
Labudda et al. (71)	10	12	2/10	6/6	57.6 (±7.83)	62.33 (±4.81)	Not stated	3	7.1 (±3.7)	Yes	Cognitive: decision
Gescheidt et al. (72)	18	18	4/14	7/11	52.67	50.61	18.89	1.97	6.33	Yes	Cognitive: decision
Schonberg et al. (73)	7	17	5/2	13/4	58.7 (±3.7)	60 (±4.1)	12.4 (±7.2)	1.9 (±0.7)	4 (±2.9)	Yes	Cognitive: error detection
Grossman et al. (74)	7	9	Not stated	Not stated	71 (±10.2)	65.7 (±10.2)	Not stated	1	Not stated	Yes	Cognitive: sentence comprehension
Ibarretxe-Bilbao et al. (75)	24	24	8/16	8/16	56.13 (±8.5)	57.58 (±8.9)	14.67 (±3.5)	1.73 (±0.4)	3.06 (±1.6)	Yes	Cognitive: speech
Isaacs et al. (76)	13	18	7/6	12/6	62.23 (±6.83)	68.06 (±9.52)	Not stated	1.46 (±0.52)	5.39 (±3.8)	Yes	Cognitive: speech
Sachin et al. (77)	8	6	3/8	4/8	Not stated	Not stated	Not stated	Not stated	Not stated	Yes	Cognitive: speech

(Continued)

TABLE 1 | Continued

References	PD (n)	HC (n)	f/m PD	f/m HC	PD age (±SD)	HC age (±SD)	UPDRS III	Hoehn & Yahr	Disease duration (years)	Nil-finding	Task
Nemcova et al. (78)	16	55	4/75	38/17	62.7 (±6.8)	66.7 (±7.3)	16.8 (±9.1)	Not stated	4.4 (±2.5)	Yes	Cognitive: visual object-matching task
Dan et al. (79)	25	32	10/15	17/15	64.7 (±8.3)	63.3 (±7.7)	30.4 (±11.1)	2 (±0.5)	11.9 (±4.7)	Yes	Emotional recognition task
Pohl et al. (80)	13	13	5/8	6/7	Median: 68	Median: 65	24.21 (±9.60)	Not stated	5.94 (±4.39)	Yes	Emotional recognition task
Nombela et al. (81)	10	10	9/14	10/13	60.5 (±3.45)	59.6 (±4.47)	22.2 (±7.9)	2.5 (±0.5)	8.1 (±2.0)	Yes	Executive functioning task
Rowe et al. (82)	12	12	9/15	9/12	62 (±6)	62 (±6)	33.7 (±8.54)	2.46 (±0.45)	5.4 (±3.6)	Yes	Motor and attention task
Arnold et al. (83)	20	20	8/12	8/12	63.9	64.2	26.1	1.65	5.8	Yes	Motor and cognition task
Nieuwhof et al. (84)	19	26	4/15	10/16	70.7 (±6.1)	71.2 (±5.3)	36.0 (±8.2)	2	6.2 (±4.8)	Yes	Motor and cognition task
Zhao et al. (85)	21	22	Not stated	Not stated	60.43 (±9.65)	59.23 (±11.12)	20.57 (±3.83)	1.2 (±0.3)	1.95 (±1.8)	Yes	Motor and sensory task
Sabatini et al. (86)	6	6	2/4	2/4	61 (±8)	59 (±19)	16 (±4)	2.7 (±0.5)	5 (±2)	Yes	Motor task
Matt et al. (87)	13	14	6/7	5/9	58.7 (±13)	57.4 (±9.8)	30.2 (±12.2)	2.35 (±0.32)	6.3 (±4.7)	Yes	Motor task
Tessa et al. (88)	11	10	2/9	3/7	68 (±8)	64 (±3.8)	13.5 (±4.8)	1.2 (±0.3)	1.5 (±0.5)	Yes	Motor task
Hughes et al. (89)	20	20	10/10	13/7	65.5	65.2	22.2	2.2	Not stated	Yes	Motor task
Yan et al. (90)	11	12	0/26	0/25	61.5 (±7.1)	65.5 (±10.1)	20.1 (±6.3)	Not stated	4.9 (±3.9)	Yes	Motor task
van Eimeren et al. (91)	20	10	9/11	’5/5	50.3 (±7.8)	50 (±8.7)	21.95 (±13.6)	Not stated	10.86 (±7.69)	Yes	Motor task
Spraker et al. (92)	14	14	’6/8	(mached)	57.2 (±9.6)	57.6	18 (±8.1)	1.7 (±0.45)	16.5 (±10.8)	Yes	Motor task
Bedard et al. (34)	10	10	’5/5	8/2	57.4 (±8)	62.4 (±10)	14 (±7.8)	Not stated	Not stated	Yes	Motor, sensory- and learning
Westermann et al. (93)	12	16	5/5	’6/4	57.1 (±2.2)	64.7 (±1.4)	Median: 28	Median: 2	Median: 3.3	Yes	Sensory (olfactory) task
Lefebvre et al. (94)	34	17	12/23	7/10	63.1	62.76	23.4	2 (±0.83)	8.53	Yes	Sensory (visual) task
Caminiti et al. (95)	13	12			63.3 (±6.3)	59 (±2.3)	NA	1-2	5 (±3.4)	Yes	Working memory task
Simioni et al. (96)	19	20	0/10	0/10	66 (±8.6)	65 (±6.7)	15.3 (±5.4)	2.4 (±0.7)	6.9 (±3.3)	Yes	Working memory task

F, female; HC, healthy controls; M, male; PD, Parkinson's Disease; UPDRS, Unified Parkinson's Disease Rating Scale.

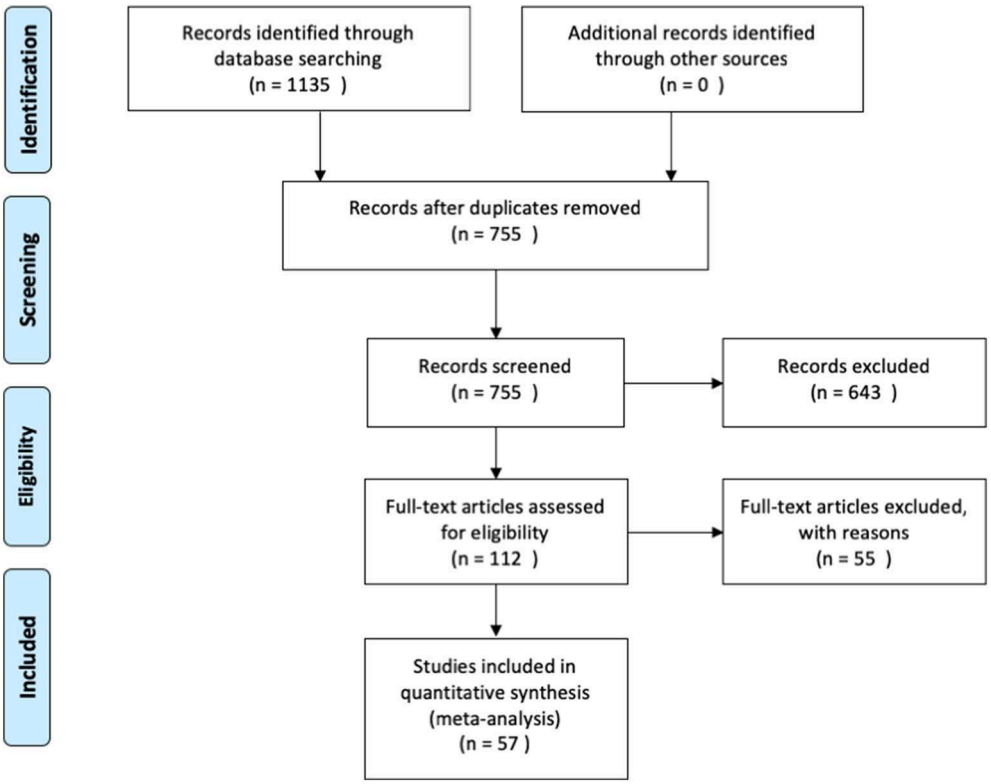

FIGURE 1 | Overview of the study identification and selection process.

medication to have a "normalizing" effect on the neural activity of PD patients (97, 98), a separate sensitivity analysis using only patients in their OFF-state (i.e., patients who were asked to stop taking medication for ∼12 h), was also carried out.

Motor Studies

In order to investigate group differences in cerebellar activation(s) specific to motor paradigms, a meta-analysis including only studies using a motor-task was also conducted. As we aimed to localize regions specifically linked to motor functioning in PD patients, only studies with reported differences (i.e., no nil-findings) were thus included in this analysis. The uncorrected threshold was kept at $p < 0.005$ with a cluster size threshold of 10 voxels.

Cognitive Studies

Likewise, a separate meta-analysis was conducted including only studies employing cognitive paradigms. Here, as before, an uncorrected threshold of $p < 0.005$ was used, with an extent threshold of 10 contiguous voxels.

Meta-Regression Analyses

Two separate regression analyses were also performed to examine the relationship between the pattern of cerebellar activations and the patient's UPDRS III motor scores, as well as the disease duration. As five studies had not defined whether the UPDRS scores referred to the motor subscale (UPDRS-III) or to the total, we thus conducted a sensitivity analysis including only those that explicitly stated that they used the motor subscale. For exploratory purposes, the threshold used for the meta-regression analyses were kept at a liberal uncorrected $p < 0.05$ and extent threshold of >10 voxels.

Finally, we used PD patients' cognitive status [assessed through scores on cognitive tests, such as the Mini Mental State Examination (MMSE) (99)] in a regression to explore the relationship between this variable and their related cerebellar activity in a meta-regression analysis.

RESULTS

Selected Studies

An overview of the study identification, screening and selection process is presented in **Figure 1**. Our search yielded a total of 755 articles after duplicate findings were removed. After further screening, 112 articles were further assessed yielding 57 articles that fulfilled the inclusion criteria. The total number of subjects across all studies included in this meta-analysis was 1856 (890 PD patients and 966 HC), with an average age of 62.07 (±4.69) and 60.69 (±6.15), respectively. The PD patient sample had an average disease duration of 5.90 (±3.05) years, an average Hoehn & Yahr score of 1.92 (±0.41), and an average UPDRS III score of 23.24 (±6.63). A summary of the study demographics can be found in **Table 1**. Of the 57 studies, 30 did not report any significant differences between PD and controls in response to either motor or cognitive paradigms. A chi-square test assessing

TABLE 2 | Results from the meta-analyses and meta-regression with their corresponding coordinates and regions.

	Region	Hemisphere	*x*	*y*	*z*	SDM-Z	*p*-value	Voxels	Peak I^2	Eggers bias	Eggers *p*-value
All studies ($n = 57$)	Crus II	L	−38	−70	−42	3.123	0.000894606	66	43.397	0.74	0.530
	Ver III/IV	L	−2	−42	−16	2.891	0.001919806	18	38.690	0.21	0.856
	Negative clusters:										
	Fusiform gyrus	R	30	−44	−18	−2.844	0.002227843	13	27.541	−0.66	0.530
	Local peaks:										
	Fusiform gyrus	R	30	−44	−18	−2.844	0.002227843				
	Lobule IV/V	R	26	−46	−22	−2.686	0.003616929				
	Lobule IV/V	R	20	−50	−28	−3.038	0.001190126	10	67.158	−3.51	0.001
OFF-state ($n = 36$)	Ver III/IV	L/bilateral	−2	−44	−14	3.332	0.000430882	59	6.574	0.68	0.635
	Local peaks:										
	Ver III	L/bilateral	−2	−42	−14	3.332	0.000430882				
	Lobule IV/V	L	−6	−54	−8	2.878	0.002003968				
	Crus II	L	−40	−66	−48	3.127	0.000883460	20	15.949	0.69	0.643
	Negative clusters:										
	Lobule IV/V	R	16	−50	−22	−3.040	0.001183808	30	42.218	−1.43	0.323
Cog studies ($n = 5$)	Lobule IV/Lobule III/Ver III	R	10	−44	−18	3.647	0.000132442	158	8.546	2.28	0.843
	Local peaks:										
	Lobule IV/Lobule III/Ver III	R	10	−44	−18	3.647	0.000132442				
	Lobule I-IV	R	8	−38	−26	3.575	0.000175357				
	Lobule I-IV	R	6	−38	−14	3.440	0.000290871				
	Lobule VIII	L	−32	−60	−48	3.027	0.001234889	88	9.701	7.87	0.353
	Local peaks:										
	Lobule VIII	L	−32	−60	−48	3.027	0.001234889	32			
	Lobule VIII	L	−18	−64	−46	2.995	0.001370609				
	Lobule VIII	L	−24	−64	−48	2.942	0.001628339				
	Lobule VIII	L	−18	−68	−48	2.942	0.001628876				
	Lobule VI/V	L	−20	−74	−18	2.891	0.001922667	11	10.196	9.66	0.229
	Local peaks:										
	Lobule VI	L	−20	−74	−18	2.891	0.001922667				
	Crus I	L	−18	−84	−26	2.592	0.004770517				
UPDRS III regression ($n = 25$)	**Negative clusters:**										
	Lobule VI	R	10	−62	−28	−2.312	0.010397077	84	3.767	−0.03	0.979
	Vermal lobule III	Bilateral	2	−74	−34	−2.189	0.014311850	49	28.736	−0.04	0.978

Local clusters refer to clusters where more than one local peak was identified. Coordinates are in MNI space.

whether the prevalence of cerebellar findings across studies was different from chance (i.e., the null hypothesis being that half the studies will show cerebellar difference and half will not) did not reach significance [$\chi 2_{(df=1)} = 0.157$, $p = 0.691$]. This indicates that—without accounting for any other variable (i.e., type of tasks, medication status, etc.)—the probability of finding differences in cerebellar BOLD activity across fMRI studies comparing PD patients and healthy controls was not different from 50%.

Meta-Analysis

Despite the fact that 30 of the studies did not report any significant differences between patients and controls in response to tasks, the general meta-analysis of all selected fMRI studies yielded significant results implicating the cerebellum, even after accounting for the nil findings. It revealed two positive activation clusters (i.e., hyperactivation in PD patients as compared to healthy controls), one predominantly covering the left Crus I and Crus II (**Table 2**, **Figure 2**) while the other cluster covered largely the vermal area of lobule III. In addition, the results revealed two negative clusters that were located over the fusiform gyrus, and lobule IV/V (**Table 2**).

Of note, almost half of the studies that reported a nil-effect (when comparing patients and controls) included participants that were scanned in the ON medication state (14/30) (status unknown in 2/30), while only three of the studies that reported a between-group effect included patients in the ON state (3/27) (status unknown in 2/27). A chi-square test assessing whether the PD patients medication status (ON vs. OFF) was associated with the prevalence of cerebellar findings across studies was significant

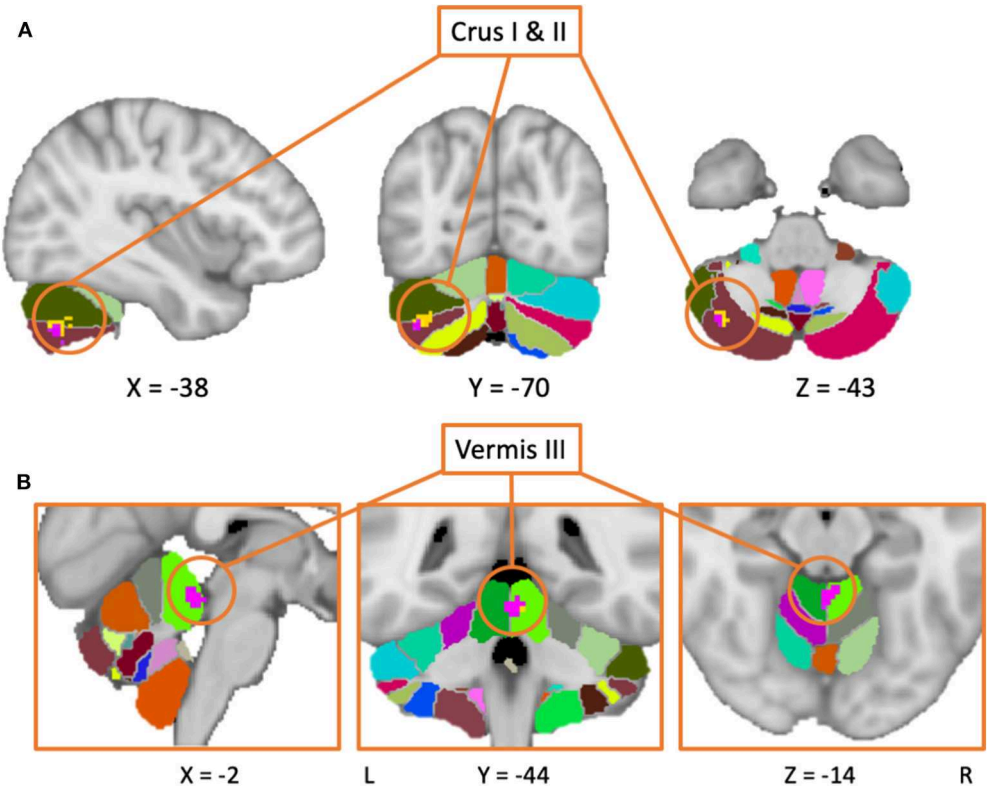

FIGURE 2 | Results from the meta-analysis including both medicated and unmedicated patients (yellow area), as well as the results including only studies with unmedicated patients (purple area) are overlaid on the MNI152 template brain with a probabilistic cerebellar atlas (39). **(A)** The clusters are mainly located in Crus II (in brown), with the larger cluster also expanding into Crus II (in olive) and lobule VI (in light green). **(B)** Both clusters are located in the vermal lobule III. In this case, the cluster from the main meta-analysis (in pink) is overlaid the larger cluster from the second meta-analysis including only patients in the OFF-state (blue cluster).

$[\chi^2_{(df=1)} = 6.202, p < 0.05]$. This indicates that one is significantly more likely to find cerebellar differences between PD patients and healthy controls across fMRI studies that included patients in the OFF state, compared to those that involved patients in the ON state. To investigate the effect of medication, a separate analysis was then performed, including only studies where patients were in the OFF-state (36 studies). This analysis yielded two positive and one negative activation clusters similar to those identified in the previous analysis when all studies were included. The largest positive cluster was located in vermal lobule III/IV, although with a smaller spatial extent as compared to the same cluster obtained in the main meta-analysis (i.e., including all studies). The other cluster was located over Crus II with some voxels extending into Crus I. Both of these activation clusters overlapped with those obtained from the main meta-analysis. As with the main analysis, the OFF-state studies also resulted in a negative cluster in lobule IV/V. **Figure 2** shows the results of both analyses overlaid on a cerebellar atlas using the MNI template brain.

Motor Studies

Thirty-one out of 57 studies used motor paradigms to assess differences in patients vs. controls; of these, 20 showed significant differences in cerebellar activation between patients and controls, and were thus included in the analysis. The meta-analysis did not reveal any significant clusters of activation related directly to differences between PD patients and healthy controls during tasks tapping into motor functioning.

Cognitive Studies

Twenty-one studies employed a cognitive task. These included paradigms that tested a variety of cognitive functions including: planning (46), cognitive control (43, 44, 70, 72, 73), attention (82), memory and working memory (48, 95, 96), executive functioning (67, 81, 84), object recognition (78), learning (34), imagery (68), decision making (71), linguistic processing (74–76, 83). However, only five studies reported significant differences between patients and controls. The meta-analysis based upon these studies revealed clusters of increased activity in PD patients in the left lobule VIII and VI and in the right lobule IV and V (see **Figure 3**), indicating that these areas are particularly implicated in cognitive functioning in PD patients.

Meta-Regressions

UPDRS

A meta-regression was conducted to examine the possible relationship between the pattern of cerebellar activity and the UPDRS scores in PD patients. Overall, the UPDRS scores (100) were listed in 25/27 studies (with nil-finding studies excluded).

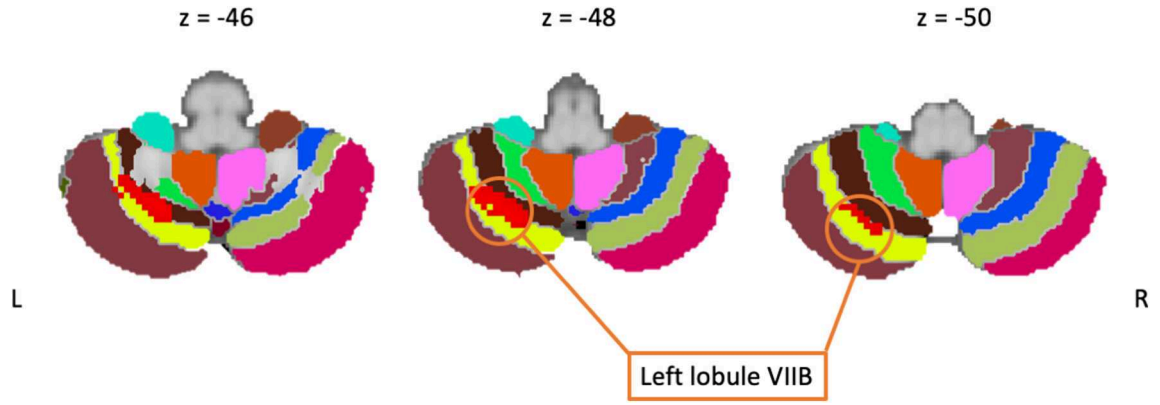

FIGURE 3 | Including only cognitive studies showed an activation cluster (red) over the left lobule VIIB (yellow), here overlaid on coronal slices of the cerebellum.

The meta-regression conducted on these studies revealed a negative correlation between the average UPDRS scores and cerebellar activation in a cluster covering the right lobule VI, suggesting that reduced level of functional activity in this area was particularly linked to the patients' motor symptomology. An additional negative correlation was found in a cluster located within the vermal lobule VIII region. Upon visual inspection, the latter cluster was shown to cover mainly the right vermal VII-VIII, with some bordering voxels in right and left Crus II. Average estimates from each study were extracted from the local peak ($x = 10$, $z = -62$, $y = -2$) and plotted against UPDRS scores, resulting in a significant correlation between the two ($r = -0.711$, $p < 0.001$) (see **Figure 4**). It is important to note that 20 out of the 25 studies reported explicitly the UPDRS III (i.e., part 3 of the UPDRS test—the motor subscale) scores. For the remaining five studies it was unclear whether the listed UPDRS scores were referring to the total score or to the motor subscale (UPDRS III). As such, we conducted a sensitivity analysis, assessing the impact of the five studies on the UPDRS correlation. When these five studies were excluded from the correlation, the Pearson correlation coefficient remained significant ($r = -0.728$, $p < 0.001$).

Disease Duration

Disease duration (in years) was reported in 22/27 studies (with nil-finding studies excluded). The meta-regression examining the relationship between cerebellar functional differences in PD compared to HC during both motor and cognitive paradigms revealed no significant correlation with disease duration.

Cognitive Functioning

We examined the reported cognitive scores (either MMSE or MOCA) from each study with the intent of conducting a meta-regression analysis involving the PD patients' level of cognitive functioning and their general pattern of cerebellar activation. The average MMSE scores reported in the 22 studies, in which cognitive measures were stated, was 28.6 (STD:1) (of a total of 30). Most studies used MMSE cut-off scores (most often a cut-off of 26/30) as an inclusion/exclusion criterion in order to avoid including PD patients with cognitive decline, while in some studies the MMSE or Montreal Cognitive Assessment [MoCA (101)] scores were not indicated, hence resulting in a limited spread of the scores in the studies where these were reported. Including cognitive scores in the meta-analysis could therefore have been a source of bias. Consequently, we opted against conducting a meta-regression with these scores.

DISCUSSION

This is the first meta-analysis of functional neuroimaging studies that aimed to quantify task-related differences in cerebellar neural activity in PD patients relative to healthy controls. Our findings reveal that PD patients showed hyperactivity in Crus I and II, as well as in lobule I—IV, across studies that used both motor and non-motor (i.e., cognitive) paradigms. Furthermore, results from the meta-regressions showed that the functional changes found in cerebellar regions VI, and vermal lobule VII and VIII correlate negatively with UPDRS scores. Together, such findings provide support for the functional specificity of the cerebellum in relation to the disease, as discussed in detailed below.

Overall Hyperactivation in PD Patients

The meta-analysis including all studies (both motor and non-motor paradigms) revealed a cluster of increased activation over the right Crus I and II in PD patients compared to controls. This pattern was evident even when the analysis was performed using only studies with patients in their OFF-state, hence indicating that this result does not depend on the medication status.

Lobules Crus I and II have been referred to as a part of the "cognitive cerebellum" (37, 102). This notion is based upon the following three lines of evidence; first, from non-human primate studies that found direct anatomical connections to exist between these cerebellar sub-regions and the pre-frontal cortex (103); second, from previous reports in humans using resting state functional connectivity analyses where connectivity between Crus I and II with the dorsolateral pre-frontal cortex (DLPFC) and anterior pre-frontal cortex (APFC) has been

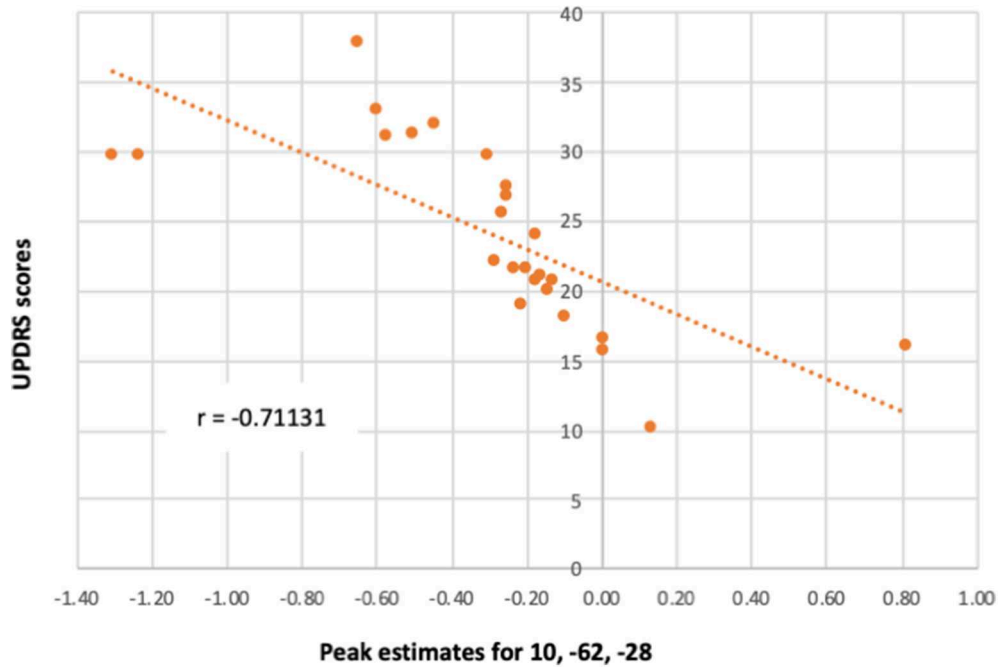

FIGURE 4 | A meta-regression assessed the relationship between PD cerebellar activity in response to all paradigms with patients' UPDRS III scores. The figure illustrates the correlation between UPDRS III scores and each study's estimates of the activity in lobule VI from the local peak in the cluster 10, −62, −28.

observed (26, 37, 104–106); and finally, from a meta-analysis of neuroimaging activation studies on cerebellar functional topography in healthy individuals that provided evidence that Crus I and II are frequently activated during cognitive tasks (107).

Both structural and functional studies in groups of PD patients also support the role of Crus I and II in cognitive functioning. For instance, a meta-analysis on gray matter changes in neurodegenerative disorders reported that PD patients showing evidence of a cognitive impairment most frequently also presented a reduction in cerebellar gray matter, while no atrophy in motor regions of the cerebellum was found (26). Furthermore, another structural study showed that gray matter alterations in Crus I can be used to classify between PD patients and matched control subjects with a 95% accuracy (108). Finally, using fMRI, a study in which healthy controls and PD patients executed a motor timing task requiring cognitive demands, the authors reported increased activation in both Crus I and II in PD compared to controls (31). Together, these findings are thus in accord with our results that Crus I and II are overactive in PD patients compared to controls, and that the cerebellar hyperactivation may be linked to cognitive functioning in PD.

Our meta-analysis included almost twice as many studies that focused on "motor" compared to "cognitive" functions. However, the observed hyperactivation in the "cognitive cerebellum" described above is unlikely to represent pure motor or pure cognitive functioning, but rather a more non-specific overactivity in PD patients compared to controls, irrespective of the task. If we consider that some of the motor studies in the current meta-analysis included also sensory components, i.e., auditory (31), tactile (85), and pain processing (66), the idea that hyperactivity in Crus I and II in PD patients is not strictly linked to motor functioning seems to receive more support. Indeed, the lack of relationship between the UPDRS motor scores and Crus I and II functional activity also supports this notion. Thus, although the underlying basis for this hyperactivity is not easy to pinpoint, one could speculate that it reflects a compensatory response to basal ganglia dysfunction.

Finally, our findings revealed a cluster of hyperactivity on the border of the hemispheric and vermal lobule III area, a region linked to sensorimotor/vestibular function (26, 31). Interestingly, a link between symptoms of ataxia and damage to areas II-V of the cerebellum has previously been reported (109). Thus, given that both disorders are associated with problems of balance and postural instability, this could explain why we observed such overactivity within this sub-region in PD patients. Consistent with this interpretation is also the fact that the same activation clusters were obtained when we included the studies investigating only patients in the OFF state in the analysis.

Cognitive Paradigms Are Linked to PD Hyperactivity in Lobules VI and VIII

When including only studies that employed cognitive paradigms in the meta-analysis, our results revealed stronger activations

in lobule VI and VIII in PD patients as compared to controls. Even though both lobules VI and VIII are thought to be part of the cerebellar homunculus (110) and are considered as "motor lobules" due to their anatomical projections to the motor cortex (111, 112), there is also evidence that they contribute to cognitive functions as well. For instance, these lobules have been found to be involved in executive functioning (107) as well as spatial, language and verbal processing (VI) (107) in healthy individuals through their functional connectivity with the APFC and DLPFC (104, 105). Moreover, reciprocal connections between these regions have been described in non-human primates (103). Taken together, these findings thus provide support to the idea that our results reflect a hyperactivation of lobules VI and VIII in PD in response to the cognitive demands of the task, such as working memory and other executive functions. The meta-analysis also resulted in a cluster of activation over lobules IV/V. Both lobules have functional connections to the sensorimotor cortex (36), while studies in non-human primates have also provided evidence for anatomical projections between these two regions (103). Lobule IV and V moreover show a topographical sensorimotor representation that is frequently activated during sensory or motor engagement (113). A cluster of activity over this area in response to cognitive paradigms is thus not unexpected, as most cognitive paradigms carried out in the scanner also requires sensory and motor processing. Stimuli are normally presented with a visual or auditory modality, prompting a motoric feedback, usually with a hand response. While it is true that, in most of these studies that used cognitive paradigms, the behavioral performance of PD patients was impaired relative to healthy controls, hence suggesting that the cerebellar hyperactivation may reflect functional impairment, there were no reported correlations (either positive or negative) between cerebellar activation and behavioral performance. Therefore, besides concluding that this hyperactivation seems to be in response to the cognitive demands of the tasks, our review of the current neuroimaging evidence cannot provide a proper interpretation of its functional role, nor determine whether the pattern of activity reflects a pathological or compensatory mechanism.

Motor Paradigms Did Not Reveal Any Significant Group Differences in Cerebellar Activation

Twenty studies were identified using motor paradigms and were included in a separate meta-analysis. However, the latter did not result in any significant clusters of cerebellar activation that would indicate a differential functional involvement of this structure when comparing the PD patients with their healthy counterparts across a variety of motor paradigms. A closer examination of these studies indicates, however, that the lack of a significant group difference may be due to the fact that 12 studies reported cerebellar hyperactivations in PD relative to healthy controls, with 8 studies presenting the opposite pattern. It is also important to note that most of these studies did not report significant differences in motor performance between the two groups (this was, in some cases, by design, because all subjects were trained to reach a certain performance level prior to the fMRI session). Thus, it is possible that differences in motor functioning between PD and controls cannot be linked reliably to specific cerebellar sub-regions at the current time, perhaps due to the variation of tasks utilized by the studies included in the meta-analysis. Yet despite the lack of a significant result in this meta-analysis, several useful observations can be drawn from a descriptive analysis of these 20 studies that employed motor paradigms and nevertheless reported significant group differences at the study level. The first observation is that 9 of the 12 studies that reported cerebellar hyperactivations in PD also used paradigms with rhythmic tapping or sequential movements tasks, with the remaining 3 using motor tasks that had a strong cognitive component to it, such as predictive motor timing (51), controlled thumb pressing movements (31), and center-out step-tracking (60). The second is that of the eight studies that reported hypoactivations, half used grip force tasks and the other half required participants to produce various types of sequential or ballistic movements. As such, we can observe that hyperactivations tend to be associated with tasks that had significant cognitive demands, thus supporting the idea that the hyperactivations seen in our general meta-analysis combining motor and cognitive paradigms are likely to reflect the general cognitive task demands.

UPDRS III Scores Are Negatively Linked to Activity in Lobule VI and Vermal VII and VIII

The meta-regression revealed a negative relationship in PD patients between the UPDRS scores and the cerebellar activity in lobule VI, Crus II and vermal lobules VII/VIII, hence suggesting that patients with the worse motor clinical states also had reduced activity in these areas. The link between the patients' symptoms measured with the UPDRS III and functional activation in these regions can be explained by the known neuroanatomical connections between the cerebellum and the cerebral cortex. For instance, lobule VI is a part of the cerebellar homunculus and is known to have functional and anatomical connections to the sensorimotor system (26, 37, 114–116). Interestingly, the volume of lobule VI has also been shown to correlate positively with motor functioning (dexterity, grip force, coordination and finger tapping speed) in older adults (117). Similarly, anatomical connections between vermal lobules V—VIIIB and the primary motor cortex have been reported and are hypothesized to play a significant role in both active movements and posture (118). Thus, together, these findings may explain the negative association between the activity in vermal lobules VII and VIII and the UPDRS scores through the connections between these cerebellar regions and the sensorimotor system. If this is the case, then the reduction of functional activity in vermis and lobule VI might be the main cerebellar perpetrators involved with the worsening of motor symptoms.

Although PD motor symptoms tend to worsen as the disease progresses, the meta-regression with disease duration did not reveal any significant association with cerebellar activity using the studies considered in the current meta-analysis. One interpretation of this result could be that the mean disease

duration reported in these studies is not a very good proxy of disease severity. Indeed, several factors could explain both intra- and inter-study variability in this regard. For instance, it is expected that patients deteriorate at different rates, are diagnosed at various ages and stages of the disease, and have different lifestyles. Moreover, while the average disease duration in the studies included in the meta-analysis ranged between 0.19 and 6.5 years, most studies included only patients in stages I and II (119). By contrast, if one considers that the average disease duration constitutes an adequate proxy of disease severity, the lack of correlation between it and cerebellar activation could again be interpreted as reflecting a compensatory mechanism of the cerebellum. As such, it is conceivable that this mechanism could be set in effect as early as the basal ganglia ceases to function optimally, and that its effectiveness reaches an asymptote when it is unable to engage more resources. Alternatively and as suggested by Wu and Hallett (41), it is also possible that the cerebellum reaches a compensatory peak activity early in the disease, but wears off as the disease progresses and its efforts become futile. Finally, another reason for the lack of correlation with disease duration is the notion that certain changes in cerebellar activity in PD are more directly related to specific symptoms of the disease (120–123), and even influenced by dopaminergic medication as suggested by Mirdamadi (40). Previous research has shown that tremor dominant PD patients may recruit the cerebellum more so than those who are akinetic/rigid predominant (120), the latter being linked more specifically to vermal dysfunction. Although we do not have information regarding the symptom profile of the patient's included in these studies, a akinetic/rigid predominant representation could explain the negative association between the symptom severity and vermal function. Thus, the finding that the UPDRS III, and not disease duration, was found to be linked with cerebellar hypoactivity could be explained by heterogeneity of patient subtypes recruited in the studies. This could also explain why our meta-analysis yielded, not only a non-specific hyperactivity, but a hypoactivity linked to motor symptom severity as well.

Regrettably, there were insufficient data and little variability regarding the measure of cognitive functioning (MMSE or MoCA scores) to conduct an informative meta-regression to assess the relationship between the level of cerebellar activity and cognitive dysfunction in PD patients. Understandably, many studies used cognition scores as a screening measure in order to exclude patients with signs of significant cognitive dysfunction. Thus, a proper assessment of the relationship between cognitive decline and the cerebellum should be the focus of future research. Interestingly, a previous study examined the neural activity of PD patients with and without mild cognitive impairment (MCI) over time, and found that PD patients with MCI showed increased cerebellar activity (mainly Crus I) in the follow-up test, which was not seen in PD patients without MCI (124). This finding further adds to the involvement of Crus I in cognitive functioning in PD patients, and argues for a progressive involvement of cerebellar activity with cognitive function/dysfunction.

Limitations

By design, our review focused only on task-related activation studies. As such, we did not cover other functional neuroimaging approaches, such as resting-state, which might have provided additional information. A systematic analysis of the results based on this modality is yet to be done, and could bring valuable insight into the role of cerebellum in PD.

This review, as with most studies on PD, is faced with the problem of heterogeneity across studies, both in terms of experimental paradigms and patient samples. The clinical presentation varies from patient to patient, each presenting with different types of symptoms as well as the level of severity of both motor and non-motor symptoms. Although we made efforts to keep the studies as similar as possible, we could not control for the within-study heterogeneity. Moreover, because we aimed to be as inclusive as possible in our meta-analysis, including studies with and without nil-findings from whole-brain and ROI analyses, we can be more certain that the results obtained from this study reflect true differences. Another challenge when reviewing articles in a research domain like the one discussed here, is the difference in methodology and outcome measures used in the respective studies. This is problematic as it makes study comparisons and interpretations more difficult. Prospective studies should therefore aim to use standardized and/or well-established methods and outcome measurements.

CONCLUSIONS

The current review provides valuable insight into the functional role of the cerebellum in PD, in regards to both motor and non-motor functioning. We were able to quantify the current cerebellar findings from the PD task induced fMRI literature, which revealed that an overall hyperactivity is seen in Crus I and II in response to both motor and non-motor paradigms, whereas hypoactivity in lobule VI and Crus II is linked to motor symptoms. These results suggest that certain cerebellar regions show a special implication in motor and non-motor functioning in PD, and that they are linked to the motoric clinical state, but not disease duration. Moreover, the negative correlation between the UPDRS scores and cerebellar activation in lobule VI, Crus II and vermal lobules VII/VIII, together with the lack of a significant correlation with disease duration, provide support for the view that the pattern of cerebellar activity may represent a compensatory mechanism for the basal ganglia dysfunction, where movement impairments place more demands on certain cerebellar sub-regions than others. However, this hypothesis can only be tested in a longitudinal setting and by including more severe PD populations, with specific symptomatic subgroups.

Furthermore, the present systematic review has identified several knowledge gaps and important issues that need to be addressed by future neuroimaging research using task-based paradigms in PD patients. There is a need for future studies that should include patients at a later stage in the disease, as well as longitudinal investigations of brain activity in general, and cerebellar activity in particular. This will shed more light on how

the pathology progresses and compensatory mechanisms unfold, as well as how these will impact the functional organization of the cerebellum in response to specific cognitive and motor demands. There is also a paucity of studies investigating the functional changes and reorganization of brain activity in PD in relation to pharmacological management of the disease over time. Finally, patient heterogeneity remains another important challenge that could be addressed by undertaking a better stratification of patients based on their disease pathology and symptomology, though understandably this may pose a challenge due to practical difficulties of including patients with a more advanced clinical state.

In conclusion, our study provides a review of task-based neuroimaging studies in PD with a focus on the functional specificity of the cerebellum. We show that the cerebellum in PD patients are hyperactive compared to healthy controls, irrespective of the task. We also show that cognitive functioning in PD is linked to the more recently developed cerebellar regions (i.e., Crus I and II, as well as lobule VI and VIII). In contrast, we also show that a lack of activity in motor related regions (lobule VI and vermal VII) is associated with motor symptoms severity. Together, these findings provide the first ever quantitative assessment of functional cerebellar involvement in PD patients, and importantly link various clinical aspects of the disease with specific sub-regions of the cerebellum.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

LS contributed with the conception, design, analyses, interpretation, and write-up of the first draft of the manuscript. OL contributed with the scientific input, analyses, interpretation, and wrote sections of the manuscript. JD contributed with the interpretation and scientific input. All authors contributed actively in revisions of the manuscript, as well as approving the final, submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00127/full#supplementary-material

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Functional Connectivity Changes in Obsessive–Compulsive Disorder Correspond to Interference Control and Obsessions Severity

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Introduction: Deficits in neurocognitive mechanisms such as inhibition control and cognitive flexibility have been suggested to mediate the symptoms in obsessive–compulsive disorder (OCD). These mechanisms are proposedly controlled by the "affective" and "executive" orbitofronto-striato-thalamo-cortical (CSTC) circuits with well-documented morphological and functional alterations in OCD that are associated with OCD symptoms. The precuneus region has been suggested in OCD as another key structure associated with the mechanism of "thought–action fusion." Our study aimed to elucidate the association of the altered functional coupling of the CSTC nodes (and precuneus), the OCD symptoms, and interference control/cognitive flexibility.

Methods: In a group of 36 (17 medicated and 19 drug-free) OCD patients and matched healthy volunteers, we tested functional connectivity (FC) within the constituents of the dorsolateral prefrontal cortex "executive" CSTC, the orbitofrontal cortex/anterior cingulate "affective" CSTC, and precuneus. The functional connections showing the strongest effects were subsequently entered as explanatory variables to multiple regression analyses to identify possible associations between observed alterations of functional coupling and cognitive (Stroop test) and clinical measures (obsessions, compulsions, and anxiety level).

Results: We observed increased FC (FWE $p < 0.05$ corr.) between CSTC seeds and regions of the parieto-occipital cortex, and between the precuneus and the angular gyrus and dorsolateral prefrontal cortex. Decreased FC was observed within the CSTC loop (caudate nucleus and thalamus) and between the anterior cingulate cortex and the limbic lobe. Linear regression identified a relationship between the altered functional coupling of thalamus with the right somatomotor parietal cortex and the Stroop color–word score. Similar association of thalamus FC has been identified also for obsessions severity. No association was observed for compulsions and anxiety.

Conclusions: Our findings demonstrate altered FC in OCD patients with a prevailing increase in FC originating in CSTC regions toward other cortical areas, and a decrease in FC within the constituents of CSTC loops. Moreover, our results support the role of

precuneus in OCD. The association of the cognitive and clinical symptoms with the FC between the thalamus and somatomotor cortex indicates that cognitive flexibility and inhibitory control are strongly linked and both mechanisms might contribute to the symptomatology of OCD.

Keywords: obsessive–compulsive disorder, functional connectivity, resting state, inhibitory/interference control, Stroop test, obsessions and compulsions, anxiety

INTRODUCTION

Obsessive–compulsive disorder (OCD) is a chronic neuropsychiatric disorder characterized by recurrent thoughts (obsessions) and by repetitive behavior (compulsions) that is often reported to "neutralize" obsessions and temporarily reduce anxiety (1). Generally, OCD symptoms have been proposed to be mediated by the impaired response inhibition [(2) e.g., (3) meta-analyses by Norman et al. (4)], defined as an ability to suppress pre-potent behavior that is inappropriate or no longer required (5). Affected inhibitory control in OCD, typically demonstrated as difficulty to inhibit irrelevant or distracting information (obsessive thought) and/or behavioral response (e.g., motor rituals) (3). However, alterations proposed in OCD include both inhibitory control (inhibition of motor responses in means of increased impulsivity and/or compulsivity) and the cognitive flexibility processes defined as an ability to shift the focus of attention (6, 7) and/or recognize and handle conflicting information (competition of relevant and irrelevant stimuli) (8). In fact, the inhibitory control could be affected at three consecutive stages of inhibitory control, the early interference control (closely associated with the cognitive flexibility in means of maintenance of conflicting information), the intermediate action restraint/suppression, and the late process of action cancelation (3, 9). Impaired inhibitory control has been reported in OCD patients on all three stages (10), assessed mostly by variants of the Stroop color–word test (SCWT) (7, 11–13), or alternatively by the Go/No-go tasks [e.g., (14)] and the Stop signal tasks [e.g., (15)], measuring interference control, action restraint, and action cancellation, respectively. Even though the impairment in later inhibitory processes of action restraint and action cancelation has not been previously associated with symptom severity (14, 15), it was suggested that the slower reaction times in similar tasks are related to the "not just right experience" reported by the patients (14). Moreover, the fact that motor response is not required to perform compulsion (existence of "pure obsessional" OCD type with primary obsessions and mental form of compulsions, e.g., silently counting or reassurance seeking; (16) points out toward the possibility of primary impairment already at the early stage of inhibitory control (interference control) preceding the perceivable behavioral response. However, the alternative attractor model of OCD by Rolls (17) suggests that impaired interference control reported in OCD results from affected cognitive flexibility associated with the necessary attentional shift (e.g., toward different aspects of the stimuli), suggesting impairment of executive and not inhibitory cognitive processes. However, we argue that these inhibitory and executive cognitive processes cannot be fully separated when using cognitive/behavioral tasks.

Neuroimaging studies have indicated that cognitive flexibility is mainly controlled by the prefrontal cortex (PFC) and frontoparietal attentional network [e.g., (18)]; current reviews suggest the role of fronto-hippocampal communication (19). The interference control and motor response inhibition are both dependent on cortico–striato–thalamo–cortical (CSTC) circuits [for review, see (3, 20)] intensively studied in OCD (21–24). The CSTC loops originate in the PFC and then project to the striatum, from the striatum [via the caudate nucleus (CN)] to the thalamus (THA), and finally from the THA back to the frontal cortex. With special regard to different PFC constituents of these loops, two critical CSTC circuits have been conceptualized as dysregulated in OCD: the "executive" dorsolateral prefrontal cortex (DLPFC)–striatal loop and the "affective" orbitofronto-striatal circuit [orbitofrontal cortex (OFC), anterior cingulate cortex (ACC)], with THA and striatum (CN) belonging to both of them (20). The critical role of CSTC circuits in pathophysiology of OCD has been documented using the fMRI functional connectivity (FC) approach that enables one to investigate how constituents of CSTC networks are integrated and coordinated, and to determine disorder- or symptom-specific disruptions within these networks. Most FC studies have documented that OCD patients exert increased functional coupling within CSTC loops (25–29) and that successful treatment is associated with reduced resting activity within the CSTC loop (30). Particular interest has been recently dedicated to the anterior cingulate cortex region. Structural and functional ACC alterations in OCD patients, including symptom-provocation-induced hyperactivity, has been repeatedly documented in our EEG studies (31, 32). The ACC hyperactivity has been previously linked to performance monitoring (33, 34) and dorsal part of ACC to error monitoring and conflict detection (both possibly contributing to the deficit in cognitive flexibility). Reported functional alterations in this region may thus play a substantial role in the generation of a feeling that "something is not right" preceding compulsions commonly reported by OCD patients (35). Indeed, the hyperconnectivity for tracts originating from ACC and lateral OFC has also been positively associated with the intensity of OCD symptoms (27, 28, 36), and this aberrant connectivity may even represent a specific endophenotype for OCD shared with their first-degree relatives (28). Despite the extensively documented functional alterations of the CSTC loops in OCD, it is not clear how these FC abnormalities (in terms of increased/decreased FC within this network and in outward connections originating from these loops) are associated with specific OCD symptoms. Moreover, studies that would draw

TABLE 1 | Summary table of demographic characteristics for individual age groups.

Demographic		OCD ($N = 36$)	Controls ($N = 36$)	Group difference	
		Mean score (SD)/ Sample distribution		*t*-test /Cramer's *V*/Mann–Whitney *U*	*p*-value
Age		33.26 (8.23)	33.26 (6.74)	$t = 0.35$	0.72
Sex	Males	18	19	$V = 0.05$	0.82
	Females	18	17		
Education (Years)		16.34 (2.84)	17.67 (3.63)	$t = 1.67$	0.10

a direct link between FC abnormalities in CSTC loop and alterations of cognitive flexibility and inhibitory control processes (suggested as key neurocognitive mechanisms mediating the OCD symptoms (3, 37) are inconclusive, showing both hyper- and hypo-connectivity patterns.

Even though precuneus (PCU) is not a traditional part of the CSTC loops, it has also been suggested as another key structure in OCD. It is densely projecting to PFC and plays a role in so-called thought–action fusion (38, 39) understood as cognitive bias in which an individual believes that specific thoughts and actions are inextricably linked. The fact that OCD patients are particularly prone to this bias (40–42) corresponds to recent structural and functional neuroimaging findings that support the association between OCD symptoms and the alterations reported in PCU such as gray matter reductions (43, 44) and increased precuneal activity (45) corresponding to intensity of symptomatology (46).

However, the relationship between the fundamental processes of inhibitory control and cognitive flexibility suggested to be altered in OCD and the mechanism of thought–action fusion linked to PCU alterations was not directly examined.

Functional alterations within the CSTC loop were repeatedly demonstrated in OCD patients and are still regarded as a central psychopathological mechanism of OCD (29). However, results of resting-state FC studies are often contradictory and they often show no association between FC alterations and symptom severity and/or measured cognitive performance. Our study therefore aimed to answer how altered FC is linked to OCD symptoms and cognitive mechanisms measured by the Stroop test. To this end, firstly, we systematically evaluated FC within regions with structural abnormalities in OCD documented in previous meta-analyses (47, 48) and mega-analyses (21). This set contained the major nodes of two CSTC loops recently identified as crucial for OCD (20). Concretely, we compared patients and control subjects in FC of the "executive" dorsolateral PFC-striatal loop (DLPFC) and the "affective" orbitofronto-striatal circuit (OFC, ACC), THA and striatum (CN) belonging to both of them, and PCU linked to thought–action fusion. Secondly, we tested whether the strength of these OCD-related FC alterations explains the inter-subject variability of cognitive (Stroop score) and clinical symptoms (obsessions and compulsions, and less specific anxiety) in OCD patients. In addition, we also compared medicated and unmedicated OCD patients to evaluate the influence of antidepressants on FC.

Given the previous findings, we hypothesized that FC would be increased in all preselected regions of interest (ROIs). We also expected that FC changes in frontal areas including ACC and DLPFC (responsible for attentional set shift and/or inhibitory control/error monitoring respectively) would correlate with the Stroop test score, while the striatum, thalamus, and precuneus would correlate with clinical symptoms, and none of the FC changes would correlate with the anxiety score.

METHODS

Participants

In total, 36 in-patients diagnosed with OCD according to ICD-10 (49) and DSM-IV (50) criteria and 36 healthy controls matched for age and sex (see **Table 1**) were included in the study (all right-handed). Exclusion criteria for all of the subjects involved concurrent severe or chronic medical disease, substance abuse, mental retardation, organic mental disorder, lifetime history of psychosis, mood disorders, severe head injury, and neurosurgery. Healthy controls were also required to have no history of any mental disorder or psychotropic medication use.

The severity of obsessions and compulsions in patients was assessed on the day of fMRI session using the Yale–Brown Obsessive–Compulsive Scale [Y-BOCS; (51)] and current anxiety was evaluated by the Hamilton Anxiety Rating Scale [HAM-A, (52)]. The study was approved by the local Ethical Committee and an informed consent was obtained from all of the subjects.

The patients were recruited during the initial phases of the cognitive–behavioral therapy program combining both inpatients and day-care patients. All patients were symptomatic at the time of MRI scanning as evaluated by the Y-BOCS scale, with 1—mild ($n = 3$), 2—moderate ($n = 21$), or 3—severe ($n = 10$) clinical symptoms present. In respect to major symptom dimensions of OCD, recruited patients showed most prevalent dimensions of "contamination/washing" ($n = 18$), "harm/checking" ($n = 15$), and "symmetry/ordering" ($n = 3$).

Nineteen OCD patients were either drug-free or the medication was discontinued at least 5 days prior to measurement. Seventeen patients were medicated with antidepressants (venlafaxin 250 mg, sertraline 50–300 mg, escitalopram 15–40 mg, paroxetine 40 mg, and citalopram 20 mg) and their medication status was stable for at least 4 weeks prior to the study. The patients did not use antipsychotics (occasionally used to augment antidepressant treatment in OCD)

at least 5 days prior to scanning. Only short-acting zolpidem was allowed for insomnia. On the day of fMRI, no psychotropic medication was administered before scanning. While all three patients with mild symptoms were in the subgroup of drug-free patients, 8 of 10 patients with severe symptomatology were recruited as medicated; patients with moderate symptomatology were equally distributed to both patients' subgroups (10/11).

The Stroop Color–Word Test

SCWT is a well-established task (53, 54) for assessing executive functions such as selective attention and interference control. The task was validated in the Czech version (55). It consists of three subtasks/conditions. Firstly, the participant is required to read as many words in the black ink denoting colors as possible. Secondly, the participant is required to name the colors of the displayed stimuli (non-words). The last (interference) task of the test consists of the color–words that are incongruently colored (e.g., the word *red* printed in blue ink). The participant is asked to name the color of the word while trying to inhibit the interference of the automatic tendency of reading the word. Response time in the last condition is slowed because of the competing processing of semantic and visual content of the stimuli. Each card has 100 stimuli to read/name. In the case of finishing before the time limit of 45 s, a participant starts naming from the beginning again. During the task, the participant is corrected if making a mistake. The final scores were calculated as the correct answers achieved in 45 s for each of the subtests: word reading score (W), color naming score (C), and color–word naming score (CW).

rs-fMRI Data Acquisition

Imaging data were acquired on a 3T Siemens Prisma MRI scanner (Siemens, Erlangen, Germany) equipped with a standard 64-channel head coil. Resting state fMRI (rs-fMRI) was measured with a gradient echo echo-planar sequence (GRE-EPI, TR = 2000 ms, TE = 30 ms, flip angle 70°, bandwidth 2 170 Hz/pixel, without parallel acceleration, FOV = 192 mm × 192 mm, matrix size 64 × 64, voxel size 3 × 3 × 3 mm, each volume with 37 axial slices without an inter-slice gap, a total of 300 volumes). Whole-brain anatomical scans were also acquired using a 3D T1-weighted magnetization-prepared gradient echo sequence (MP-RAGE), consisting of 240 sagittal slices with a resolution of 0.7 × 0.7 × 0.7 mm^3 (TR/TE/TI = 2400/2.34/1000 ms, FOV = 224 mm), which was used for spatial normalization and anatomical reference.

Pre-processing of the rs-fMRI Data and FC Analysis and Statistics

FC was analyzed using a seed-driven approach with the latest version (v.17.f) of CONN connectivity software (www.nitrc.org/projects/conn/). The fMRI data were corrected for head movement, together with anatomical scans, and were normalized into standard MNI space and segmented into gray matter, white matter, and CSF tissue classes using SPM12 unified segmentation and normalization procedure (56) and spatially smoothed with a Gaussian kernel (8 mm at full width half-maximum). Physiologic and other spurious sources of noise (the five strongest components of the signal from a region in the cerebrospinal fluid and the region of white matter) were estimated using the implemented component-based method and removed together with movement-related covariates (57). The residual BOLD time course of each voxel was thus obtained from the preprocessed BOLD time series by orthogonalizing it with respect to the tentative confounds [CSF, white matter, realignment parameters, identifiers of outlier scans detected during the outlier identification preprocessing step (corresponding to so-called motion scrubbing), constant and linear BOLD signal trends within each session] and further applying a band-pass filter over a low-frequency window of interest (0.008–0.09 Hz).

The FC analysis proceeded in two steps: first, the relevant functional connections were identified by starting from six key seeds; secondly, the inter-individual differences in strengths of these key connections were analyzed. To establish the overall FC of the network, we used the following bilateral seeds: **OFC**—Orbitofrontal cortex, **DLPFC**—Dorsolateral prefrontal cortex (Superior and Middle frontal gyrus), **ACC**—Anterior cingulate cortex, **CN**—Caudate nucleus, **THA**—Thalamus, and **PCU**—Precuneus. The combined Automated Anatomical Labeling (26 ROIs) and Harvard Oxford Atlas (106 ROIs) provided with the CONN toolbox was used for the FC analysis. For each region of interest (ROI), a representative signal of the ROI was obtained by averaging the residual BOLD time courses across voxels contained in the ROI. The seed-to-voxel connectivity was estimated for the selected seeds by computing Pearson correlation coefficients between the residual BOLD time courses, and further converted to approximately normally distributed Z scores using the Fisher transformation. The group effect was evaluated by *between-subject contrast* (equivalent to a two-sample t-test). The same analysis was performed for all six preselected ROIs.

To avoid a large number of false positives, for the seed-to-voxel FC mapping, we considered only findings at the conservative cluster family-wise error (FWE) corrected p level 0.05 to be significant (with cluster-forming threshold $p < 0.001$). Subsequently, we identified the coordinates of the local maxima of the most significant cluster for each of the six predefined seeds. We identified the anatomical regions (CONN anatomical parcellation) corresponding to these local maxima coordinates. The "slice display" function in the CONN toolbox was used to obtain the presented images of individual brain slices in **Figure 1**, applying the cluster-FWE corr. p level 0.05 with cluster-forming threshold $p < 0.001$ uncorr.).

The aforementioned significant clusters obtained in the seed-to-voxel analyses were exported from the CONN toolbox in a form of cluster masks representing the spatial maps of individual clusters. Similarly, in case of bilateral seeds, the masks covering both areas from the atlas were created. These masks (bilateral seeds and significant clusters) were imported to the CONN toolbox and used in the ROI-to-ROI FC analysis. Finally, Fisher-transformed Z-values quantifying the raw connectivity strength during rs-fMRI condition for region pairs (seed-cluster) were used as explanatory variables in the regression analysis in order to evaluate their possible effects on inter-subjects variability observed in cognitive interference measured by the Stroop test (see the statistical analyses below).

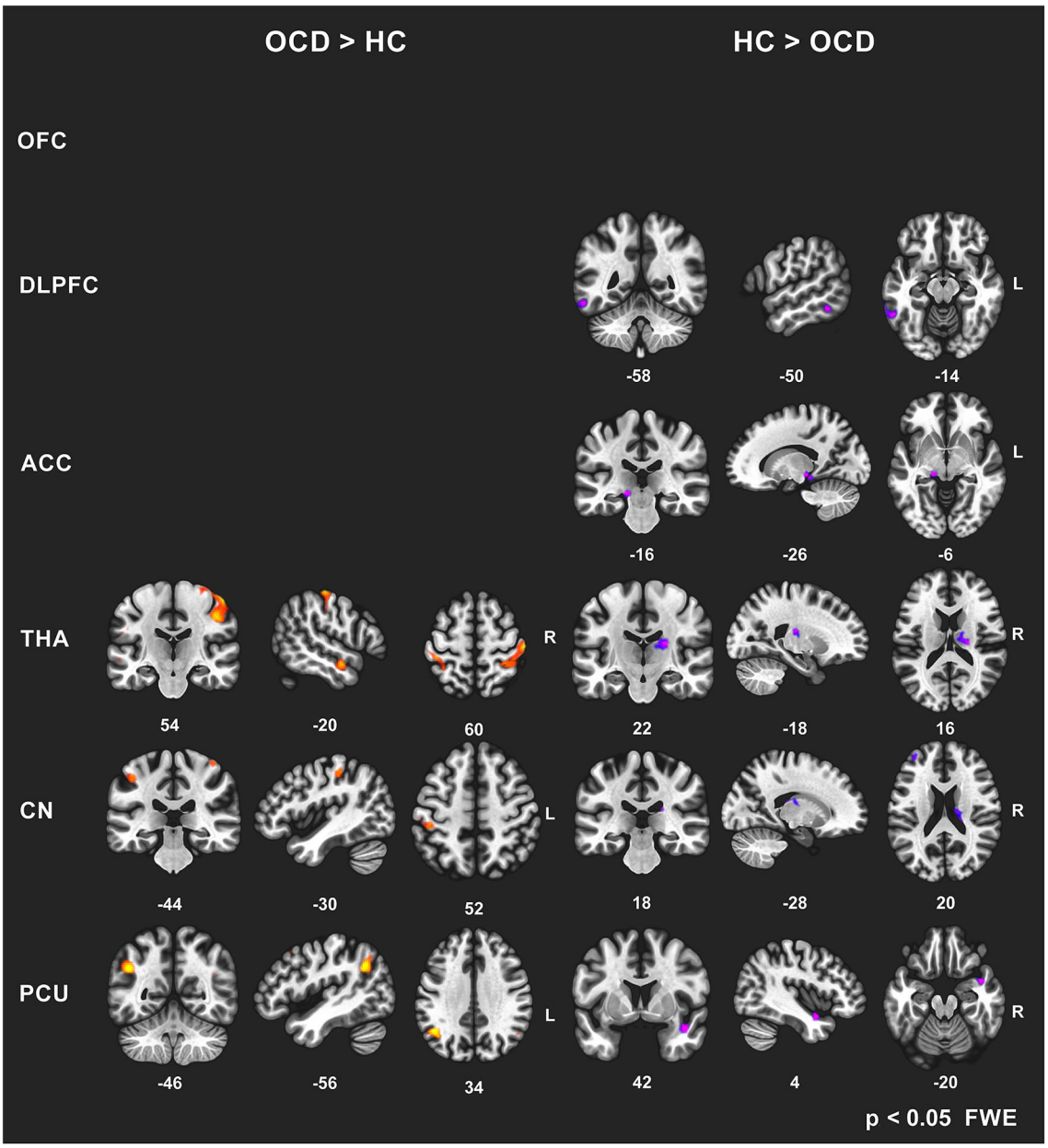

FIGURE 1 | Between-group comparisons of FC effects for individual seeds (brain slice display, FWE corr. p level 0.05, with cluster-forming threshold $p < 0.001$). Increased (OCD > HC) and decreased (HC > OCD) functional connectivity in OCD patients for six seeds (OFC—no effect found, DLPFC, ACC, THA, CN, PCU). The clusters obtained using the CONN toolbox are displayed in sagittal, coronal, and axial view in the x, y, z coordinates of the local maxima of the strongest cluster. OFC, orbitofrontal cortex; DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; THA, thalamus; CN, caudate nucleus, PCU, precuneus.

Statistica software v13 was applied in additional data analyses and the significance level was set to $p \leq 0.05$. The Student t-test was used to test between-group differences in age and education level; the Cramer's V test was applied to test between-group differences in sex distribution. The Student t-test was also used to calculate differences in FC of the identified seed-to-target (ROI-to-ROI) pairs in antidepressant-medicated and drug-free patients. The multiple stepwise regression analysis (forward) was used to evaluate whether the functional connections showing the most prominent effects of disease (one for each ROI) explain the variability observed in the cognitive (Stroop CW) and clinical (YBOC-obsession, Y-BOCS-compulsions, HAM-A) scores. We used enter/remove thresholds $F = 3.84/2.71$, approximately corresponding to $p = 0.05/0.1$ as parameters of the stepwise forward variable selection. Pearson correlation analysis was used to calculate potential associations between the cognitive measure (Stroop performance) and individual scores of applied clinical scales measuring severity of obsessions, compulsions and anxiety.

TABLE 2 | Cognitive and clinical measures.

Measured variable	OCD ($N = 36$)	Controls ($N = 33$)	Group difference	
	Mean score (SD)		*t*-test	*p*
Cognitive/stroop color–word test				
Word list (W)	88.19 (13.75)	93.15 (13.36)	1.516	0.134
Color list (C)	71.97 (12.77)	76.52 (11.12)	1.569	0.121
Color-word list (CW)	43.39 (11.56)	49.24 (9.64)	2.273	0.026*
	Mean score (SD)		**Score range (min–max)**	
Clinical/psychiatric scales				
Y-BOCS obsessions	10.40 (2.85)		5–17	
Y-BOCS compulsions	10.38 (2.80)		3–15	
HAM-A	15.63 (7.81)		3–37	

W, word list score; C, color list score; CW, color–word (interference) list score; Y-BOCS, Yale–Brown Obsessive–Compulsive Scale; HAM-A, Hamilton Anxiety Rating Scale. The asterisk symbol marks the significance level $p < 0.05$.

TABLE 3 | Increased connectivity in the OCD patients compared to HC in the selected ROIs.

OCD > HC bilat. seed	*x*	*y*	*z*	Cluster size	Cluster p-FWE	Hemi sphere	Local maxima
OFC	No effects found						
DLPFC	No effects found						
ACC	No effects found						
THA	**54**	**−20**	**60**	**1421**	**< 0.0001**	**R**	**Postcentral gyrus+**
	42	−60	−18	778	<0.0001	R	Fusiform gyrus
	−42	−32	46	774	<0.0001	L	Postcentral gyrus
	−36	−90	−14	767	<0.0001	L	Fusiform gyrus
	52	−4	−16	278	0.0016	R	Middle temporal gyrus
	−52	0	−18	245	0.0034	L	Middle temporal gyrus
	−40	−68	−18	121	0.0870^{ns}	L	Fusiform gyrus
CN	−44	−30	52	147	0.0259	L	Postcentral gyrus
	−30	−72	12	142	0.0302	L	Lateral occipital cortex
	44	−26	68	126	0.0499	R	Pre- and postcentral gyrus
PCU	**−46**	**−56**	**34**	**404**	**<0.0001**	**L**	**Angular gyrus+**
	50	−64	24	179	0.0111	R	Angular gyrus
	−44	18	54	162	0.0182	L	Middle frontal gyrus

The table shows the selected bilateral seeds and FC differences observed for comparison OCD patients > healthy controls.
x, y, z, coordinates of the local maxima; cluster size, number of voxels; cluster p-FWE, p-value FWE corrected; R or L, right or left hemisphere; local maxima, anatomical regions over the local maxima of effect; OFC, orbitofrontal cortex; DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; THA, thalamus; CN, caudate nucleus; PCU, precuneus. The two results marked in bold represent the seed-target pairs selected for the multiple regression analysis (the target clusters are marked by a plus sign). The cluster p-FWE that is statistically not significant is marked by ns.

RESULTS

The group of OCD patients differed significantly ($p < 0.05$) from the matched group of healthy controls in the "color–word naming" subtest score (incongruent word and color). The groups did not differ in the other two subtests that did not involve conflicting information (for details, see **Table 2**) or in demographic parameters (**Table 1**).

Group Differences in rs-fMRI FC

In general, we identified a prevailing increase and less pronounced decrease in FC (5544 vs. 955 voxels over FWE-$p \leq 0.05$ threshold) in the OCD sample compared to the healthy subjects. The preselected seeds showed differences in between-subject contrast (patients vs. controls, $p \leq 0.05$ FWE for all reported results, see **Figure 1** and **Table 3** for positive effects, and **Table 4** for negative effects).

TABLE 4 | Decreased connectivity in the OCD patients compared to HC in the selected ROIs.

HC > OCD bilat. seed	*x*	*y*	*z*	No. of voxels	Cluster p-FWE	Hemi sphere	Local maxima
OFC				No effects found			
DLPFC	**−58**	**−50**	**−14**	**173**	**0.0165**	**L**	**Inferior temporal gyrus**$^{+}$ (temporo-occipital portion)
ACC	**−16**	**−26**	**−6**	**145**	**0.0333**	**L**	**Hippocampus**$^{+}$
THA	22	−18	16	270	0.0019	R	Caudate and thalamus
CN	**18**	**−28**	**20**	**279**	**0.0007**	**R**	**Thalamus and putamen**$^{+}$
	−36	50	18	127	0.0483	L	Middle frontal gyrus
PCU	42	4	−20	134	0.0420	R	Superior temporal gyrus and insula

The table shows the selected bilateral seeds and FC differences observed for comparison OCD patients < healthy controls.
x, y, z, coordinates of the local maxima; cluster size, number of voxels; cluster p-FWE, p-value FWE corrected; R or L, right or left hemisphere; local maxima, anatomical regions over the local maxima of effect; OFC, orbitofrontal cortex; DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; THA, thalamus; CN, caudate nucleus; PCU, precuneus. The three results marked in bold represent the seed-target pairs selected for the multiple regression analysis (the target clusters are marked by a plus sign).

However, not all of the preselected seeds (OFC, DLPFC, ACC, CN, THA, PCU) showed a between-group difference in FC. The following efects were observed in the FC of the selected seeds using the *between-subject contrast* (patients vs. controls, $p \leq 0.05$ FWE for all reported results) in the seed-to-voxel (whole brain) approach (see **Table 3** for positive effects and **Table 4** for negative effects). Surprisingly, for the **OFC**, neither positive nor negative FC differences were observed at the level of FWE correction. In the OCD patients (compared to healthy controls), the **DLPFC** seed showed only a decrease in functional coupling with the cluster of the left temporo-occipital and posterior divisions of the inferior and middle temporal gyrus. **ACC** showed only a decrease in FC in the OCD subjects in the hippocampus and the adjacent parahippocampal cortex. In the case of the **thalamus,** highly significant effects (in the means of increased FC in the OCD patients) were found in the four main bilateral clusters consisting of the postcentral gyrus and superior parietal lobule, the fusiform and adjacent occipital cortex, and the lateral temporal cortex covering the superior and middle temporal gyri. Only a decrease in thalamic FC in the OCD patients was observed for inward thalamic voxels and the striatum. In the OCD subjects, the **caudate nucleus** showed an increase in FC in bilateral clusters of post- and precentral gyri, and one cluster located in the left inferior occipital cortex. A decrease in FC was observed in a cluster located in the subcortical gray nuclei (thalamus and putamen) and the left middle frontal gyrus. The **precuneus** showed a strong increase in FC in the OCD patients in three clusters of the bilateral angular gyrus, and the left middle frontal gyrus and less pronounced decrease in one cluster covering the right limbic lobe (superior temporal gyrus, planum temporal, and insular cortex). Given the absence of any effect of medication on FC (see below), we analyzed both medicated and unmedicated patients as one group in further analytical steps. See **Figure 1** for the most prominent positive and negative clusters for each of the seeds (apart from OFC).

For each selected seed, the functional connection showing the most prominent effect (largest cluster size) (see effects marked by bold in **Tables 3**, **4**) was used in the subsequent steps of statistical analyses with the following pairs of seed-target regions: bilateral OFC (none); bilateral DLPFC—cluster with local maxima in the Inferior temporal gyrus left; ACC—cluster with local maxima in Hippocampus left; bilateral THA—cluster with local maxima in Postcentral gyrus right; bilateral CN—cluster with local maxima in the right Thalamus; PCU—cluster with local maxima in Angular gyrus left.

Effect of Medication on FC

Antidepressant-medicated ($n = 17$) and drug-free patients ($n = 19$) showed no differences in functional seed-to-voxel connectivity (for either FWE corrected $p < 0.05$ or uncorrected $p < 0.001$ levels) or in the statistical comparison of FC values extracted for each patient for all of the five seed-target (mask) pairs. The Student *t*-tests calculated for the individual FCs (discriminating the OCD and healthy subjects) did not reveal significant differences between the medicated and unmedicated patients and the results were as follows (seed labels—local maxima of the target cluster): DLPFC—Inferior temporal gyrus left [$t_{(34)} = -0.598$, $p = 0.554$]; ACC—Hippocampus left [$t_{(34)} = -0.754$, $p = 0.456$]; THA—Postcentral gyrus right [$t_{(34)} = 0.981$, $p = 0.334$]; CN—Thalamus right [$t_{(34)} = 0.056$, $p = 0.956$]; PCU—Angular gyrus left [$t_{(34)} = -0.394$, $p = 0.696$].

Association Between the FC and Cognitive and Clinical Measures

In order to address the *a priori* tested associations between the observed effects in the OCD patients, the strongest FC differences were identified for each of the original ROIs (seeds). As no between-group effect was found for the OFC area, only the functional connections for the five remaining seeds were used as explanatory variables for the multiple regression analyses (DLPFC—Inferior temporal gyrus left, ACC—Hippocampus left, bilateral THA—Postcentral gyrus right, bilateral CN—Thalamus

right, PCU—Angular gyrus left). In order to select specific target regions, *Z* Fisher values were extracted from the ROI-to-ROI analysis, representing the seed (masks covering bilateral seeds) and the target mask covering the cluster area [labeled using the local maxima for each of the selected effects (the largest cluster size) obtained in the previous step of the between-group analysis]. The forward stepwise multiple regression analysis (with FC of the seed-target pairs used as explanatory variables) revealed a significant effect for the Stroop CW score, showing that score variability is partially explained by the FC between the thalamus and the cluster with local maxima in the right postcentral gyrus (for details, see **Table 5**). The FC between thalamus and target cluster (r. postcentral gyrus) was also associated with the severity of obsessions evaluated by Y-BOCS. No association with FC of any of the seed-target pairs was observed for the variables of other clinical symptoms (Y-BOCS compulsions, and HAM-A scores).

No significant correlations ($p > 0.05$) were identified using Pearson correlation in the OCD group between the cognitive measure (Stroop performance in the CW subtest) and the scores of applied clinical scales: Y-BOCS obsessions ($r = -0.011$, $p = 0.953$), Y-BOCS compulsions ($r = 0.186$, $p = 0.308$), and HAM-A ($r = 0.141$, $p = 0.699$). However, the clinical scales were substantially correlated, particularly the severity of compulsions correlated with the severity of obsession ($r = 0.63$, $p < 0.001$) and with evaluated anxiety symptoms ($r = 0.369$, $p = 0.032$).

DISCUSSION

The main finding of this study is the alterations of FC in the OCD patients with prevailing decrease in cortical constituents of both affective (ACC) and executive (DLPFC) CSTC loops, and both increased and decreased connections from subcortical striatal and thalamic regions and PCU. We also confirmed the altered interference control in the OCD sample. Interestingly, while the alterations observed in the FC of the thalamus are associated with altered interference control measured by the Stroop color–word subtest and severity of obsessions evaluated using the Y-BOCS scale, the FC alterations in other regions of interest did not reveal significant associations neither for interference control nor for clinical symptoms.

Interference Control (Stroop Test Performance) in the OCD Sample

Our findings of impaired performance in the subtest of the color–word list (but not in the two subtests with no conflicting information involved) in the OCD patients are in line with previous studies reporting altered interference control demonstrated by this SCWT subtest (11, 58). Even though some former studies mentioned neuropsychological slowness in OCD as a dysfunction of fronto-subcortical systems (59), we argue that this would be reflected also in the number of items correctly named during the "word reading" and "color naming" conditions of the SCWT. However, both our results and the results of other studies show equal reading speed and color naming speed for OCD patients and healthy participants (11). Affected performance particularly in the CW subtest suggests that OCD participants may have specific difficulty in maintaining the competing stimuli (color vs. word) and redirecting attention primarily allocated to the semantic meaning of the word. However, we argue that these inhibitory and executive cognitive processes cannot be fully separated, when assessed using the standard cognitive methods. Indeed, the Stroop task examines both processes, by addressing the capacity to process competing information (color vs. text) and control their maintenance (set shifting) and to inhibit irrelevant (yet primary verbal) information provided by the task. Therefore, as both may play crucial roles in the altered task performance, only association of these behavioral measures to FC alterations in OCD patients might potentially clarify their involvement.

FC Alterations in the OCD Sample

Congruently with the majority of the previous studies on FC in OCD (25–28, 36), our findings documented a prevailing increase (rather than decrease) of functional coupling in the OCD compared with healthy subjects. However, our data document increased FC specifically from bilateral striatal and thalamic regions toward cortical areas of the parietal and occipito-temporal lobe. This finding is fully in line with previous studies aimed at resting FC in OCD (60, 61). Surprisingly, we found only reduced FC originating from the cortical nodes of both executive (DLPFC) and affective (ACC) loops with negative finding in case of OFC, contrary to some of the previous reports showing only an increase in FC within CSTC regions in OCD (29). Nevertheless, this observation is in line with the results of some recent studies both in medicated (60) and in drug-free OCD patients (62), showing decreased FC within the CSTC loop and increased FC originating from central CSTC structures to the regions outside the CSTC, namely, temporal and occipital cortex and postcentral gyrus (60). While the CSTC loop alterations are suggested to be associated with behavioral regulation [e.g., inhibitory control, (60)], the increased connectivity reported outside the CSTC could be related to visuo-spatial and sensory-motor processing. The above reported decrease in DLPFC connectivity with inferior and middle temporal areas corresponds to the decreased PFC connectivity reported by Anticevic et al. (63).

Surprisingly, in contrast to previous studies [for review, see (64)], no evidence of altered connectivity in frontal regions of the OFC (another constituent of CSTC) was found. In a separate analysis, we excluded the idea that this negative finding is mediated by an artifact of medication as medicated and unmedicated patients did not differ in means of FC even at the uncorrected $p \leq 0.001$ level. We identified several interpretations for this negative finding. First, the precise location and/or type of alterations reported in this region were heterogeneous across studies, and this could affect the FC results. In concrete, the functional organization of the OFC to medial and lateral divisions of diverse cytoarchitectonic arrays (65, 66) has not been accounted for in our analysis based on recent categorization (20), in which OFC is counted as a single region. To ensure that our negative finding was not affected by the parcellation, we performed a separate *post hoc* analysis addressing separately medial (frontal pole) and lateral (anterior portion of inferior frontal gyrus) division of OFC. As we did not identify any

TABLE 5 | Results of the stepwise multiple regression analysis.

Response variable	*F*	*p*	Adjusted R^2	Explanatory variable (seed-target pair FC)	*b*	*p*
Stroop CW score	6.991	0.012*	0.146	Right THA–cluster (Postcentral gyrus right)	0.413	0.012
Y-BOCS obsessions	4.142	0.050*	0.087	Right THA–cluster (Postcentral gyrus right)	−0.339	0.050
Y-BOCS compulsions	Multiple $R = 0$, no variables entered the equation					
HAM-A	Multiple $R = 0$, no variables entered the equation					

Forward stepwise multiple regression analyses with the FC of the five strongest seed-target pairs as explanatory variables and cognitive and clinical measures as response variables calculated for the group of OCD patients (N = 36).
CW, color–word (interference) list score; Y-BOCS, Yale-Brown Obsessive–Compulsive Scale; HAM-A, Hamilton Anxiety Rating Scale; b, linear regression estimate Beta.
The asterisk symbol marks the significance level $p \leq 0.05$.

between-group differences for these regions, it is unlikely that our negative finding results from parcellation. However, we cannot exclude the role of technical factors in obtaining high-quality images in this specific region near air/tissue interfaces. Hence, due to the occurrence of susceptibility gradients, the fMRI protocol (GRE-EPI sequence) could compromise the detection of neuronal signals in OFC (67). However, we applied 3T fMRI protocol with 64-channel coil allowing the maximal resolution while covering the whole brain with improved signal/noise ratio. Some specific techniques [such as z-shim compensation; (68)] could achieve better signal detection but only in a selective volume of a single targeted region. Moreover, the strictly conservative correction (FWE) approach applied in the seed-to-voxel based analysis could weaken the chance to detect the between-group differences. We speculate that the OFC FC alterations are not sensitive to the resting state imaging protocol used in our study but that they could be unmasked by functional activation in symptom provocation protocols as in previous studies (69, 70).

Importantly, both increased and reduced FC has been reported by several previous studies for ACC, the constituent of affective CSTC loop (20, 71, 72). The reduced ACC FC with the areas of the limbic/temporal cortex in our sample is in line with recent meta-analysis revealing consistent decreased ACC connectivity with limbic areas (62), temporal cortex, and OFC (61), as well as with the hypoconnectivity within the major brain networks identified by recent meta-analysis (24).

Our findings support the suggested role of the precuneus in OCD. The increased FC of precuneus toward DLPFC and temporo-parieto-occipital junction, specifically the angular gyrus, is congruent with the role of the precuneus in symptom provocation, responsible for awareness of obsessive thoughts and visualization of compulsive actions. It has been suggested (62) that the posterior midline cortex (a part of the default-mode network) is not completely deactivated by the error-signal from the salience network (including ACC). Alternatively, it was also suggested that posterior brain regions such as the posterior cingulate cortex and precuneus may compensate for the dysregulated DLPFC–caudate–thalamus loop and its effect on cognitive flexibility (12, 73).

Together, our findings document the increased resting-state FC from bilateral striatal and thalamic regions (the subcortical nodes shared by both CSTC circuits), decreased FC of ACC and DLPFC to temporo-limbic areas, and more opposed regulatory role of PCU to anterior lateral temporal cortex (negative coupling) and more posterior temporo-parietal region such as angular gyrus (positive coupling).

Association Between Observed FC Alterations and Cognitive and Clinical Symptoms

Unexpectedly, we did not identify an association between clinical symptoms and cognitive inference and FC originating from striatal and cortical seeds. However, the hyperconnectivity of the thalamus with the somatomotor parietal cortex with local maxima in postcentral gyrus showed association both with obsession severity and with impaired cognitive interference control. This finding is not surprising as these brain areas densely connected by thalamocortical radiations are functionally responsible for speech motor control involving "feedback error detection" in sensory cortices (74, 75). Moreover, this finding corresponds to the impairment of the suggested neural mechanism of conflict monitoring at preexecution stages that activates the subthalamic nucleus, which in turn indirectly inhibits the thalamus (76–78). This would suggest the general role of thalamocortical tracts in cognitive control that plays a role in interference control during performance of the Stroop test. We propose that verbal cognitive processing (reading) of the interfering/distracting information creates a strong semantic attractor for OCD patients that repeatedly fail to shift to an alternative process (17), which is more appropriate (and adaptive) within the context of Stroop test instruction.

In line with a recent study (79), our data suggest the important role of increased coupling between thalamus and the postcentral gyrus in mediating severity of clinical symptoms, documented by convergent findings in obsessions and Stroop interference. Our results suggest that a common neuronal mechanism may underlie both cognitive and clinical scores, in means of interference control (filtering or suppression of irrelevant or intrusive information). As obsessions (intrusive thought) might be explained as representing internal speech processing, the association with the thalamo-parietal FC alterations does not seem random.

We hypothesize that FC of thalamocortical radiations shows association with OCD symptomatology even during the resting state because it is involved in the preexecution stages of feedback error detection (proactive control). On the other side, the FC

of cortical regions (constituents of the CSTCs) might be related more specifically to the clinical symptoms when measured during active state such as symptoms provocation. This assumption should be addressed in future studies comparing the strength of association between expression of clinical symptoms and FC in resting and active (provocation) states.

Alternatively, the missing association between FC alterations observed in the other CSTC regions (particularly the frontal lobe ROIs) and clinical symptoms of compulsions (and general anxiety) might be related by the complexity and variability of the compulsions. This variability could be highlighted by the fact that our OCD sample comprised an equal proportion of two OCD phenotypes (18/15)—"contamination/washing" and "harm/checking (aggressive obsessions)"—that might not be directly related to the resting-state individual FC values. Moreover, the strong correlation between the compulsion and obsession severities and moderate correlation with the rated anxiety support the concept of compulsions induced by the intrusive thought and performed to reduce the perceived anxiety.

Limitations

Some limitations to our study should be noted. Firstly, our clinical sample consisted of drug-free and antidepressant-medicated patients. However, our particular analysis did not detect any difference in FC between these groups (even at the uncorrected $p \leq 0.001$). Moreover, the effect of medication on fMRI and FC data is limited, if any (80). Secondly, to focus on the functional connections that are altered in the disease, we have used a data-driven definition of the target areas for FC from each of the preselected anatomical regions. This has the advantage of being more specific than purely anatomical definition of target regions, providing a target region that has consistently affected FC to each seed region. However, alternative thresholding of the FC maps could also be considered, leading to a more inclusive or restrictive definition of the target areas. Thirdly, the selection of the most prominent target cluster (i.e., the one with the largest cluster size) for each seed region was used for the multiple regression analyses in order to focus the analysis on the most affected functional connections. Of course, the threshold of five connections is somehow arbitrary and the inclusion of other numbers of connections obtained from the group comparison could, in principle, increase the chance of finding associations between the FC alterations and clinical symptoms; however, particularly including higher numbers of connections could increase the chance of false-positive results. Moreover, our OCD sample consisted of two prevailing OCD phenotypes that could weaken obtained findings. Due to small sample sizes, it was not possible to test potential OCD dimension-specific differences in observed FC alterations, and this should be addressed by future studies. Lastly, to address the distinction between individual stages of the inhibitory control and related cognitive abilities, the future studies should combine several cognitive tasks.

CONCLUSION

Our findings demonstrate altered resting-state FC in OCD patients. Specifically, we identified the increased FC from bilateral striatal and thalamic regions (the subcortical nodes shared by both CSTC circuits), decreased FC of ACC and DLPFC to temporo-limbic areas, and more opposed regulatory role of PCU to anterior lateral temporal cortex (negative coupling) and more posterior temporo-parietal region such as angular gyrus (positive coupling). This could be interpreted as a disconnectivity of the traditional CSTC loops in OCD counterbalanced by hyperconnectivity of CSTC regions manifested outwards. In addition, our results support the role of thalamus and its coupling with the somatomotor area of the parietal cortex in OCD, specifically in interference control and/or cognitive flexibility. Moreover, a similar association was identified also for the severity of obsessions, suggesting that suppression (filtering) of irrelevant information might be linked to the altered FC of the thalamus. We suggest that while the affected cognitive control of the conflicting information in Stroop task and severity of obsessions is linked to altered functional state and individual connections of specific brain networks, the complex behavioral clusters of compulsive symptomatology may be caused by more complex or highly individual alterations of brain dynamics that are not captured by individual connections of the studied key hubs of the CSTC network, or that even do not manifest strongly during resting brain state. Future studies should elucidate if the FC in resting and active (symptoms provocation) states differ in the strength of association with behavioral and neurocognitive expression of OCD. Moreover, these studies should separate variable OCD phenotypes (dimensions) and include a combination of methods aimed at inhibitory control and cognitive flexibility.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study procedure involving human participants and all apllied measures were reviewed and approved by the local Ethics committee of the NIMH in Klecany, Czech Republic in accordance with the Declaration of Helsinki. The patients and healthy participants provided their written informed consent to participate in this study prior to participation.

AUTHOR'S NOTE

The well-documented alterations of the orbitofronto-striato-thalamo-cortical (CSTC) circuits are considered a central psychopathological mechanism associated with the symptomatology of the obsessive-compulsive disorder (OCD). The impaired mechanisms of inhibitory control and/or cognitive flexibility have been previously suggested to be mediating the compulsive behavior in OCD, with the involvement of affective and/or executive CSTC loops. Our study aimed to investigate the resting state functional coupling of the CSTCs nodes and to elucidate how the altered functional connectivity pattern is linked to OCD symptoms and cognitive

interference control mechanism addressed by the Stroop test. Our findings confirmed altered functional connectivity (FC) pattern in OCD patients (both medicated and unmedicated) with a prevailing increase in FC originating in CSTC regions toward other cortical areas, and a decrease in FC mainly within the constituents of CSTC loops. In addition, our findings support the potential role of precuneus in OCD, a structure previously suggested in so-called thought-action fusion mechanism. Importantly, the associations identified in OCD patients between the functional connectivity of the thalamus and both obsessions severity and cognitive performance indicate that the mechanism of interference control might be linked to specific OCD symptoms, potentially mediated by the mutual constituents of affective and executive CSTC circuits.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication. Conceptualization: JHo, IF, and PS. Data Acquisition: IF, AF, EN, and PS. Formal Analysis: DG, IF, and JHl. Funding Acquisition: JHo. Methodology: IF, JHo, JK, JHl, PS, DG, and AF. Project Administration: IF, PS, and JHo. Supervision: JHo. Visualization: DG and IF. Writing-Original Draft: IF, JHo, AF, and DG. Writing and Editing: IF, JHo, JHl, DG, AF, EN, PS, and JK.

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