Received: 17 June 2021 | Accepted: 30 August 2021

DOI: 10.1111/ene.15095

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Neural correlates of self-awareness of cognitive deficits in non-demented patients with Parkinson's disease

Han Soo Yoo[1] | Hyeokjin Kwon[2] | Seok Jong Chung[1] | Young H. Sohn[1] | Jong-Min Lee[3] | Phil Hyu Lee[1,4]

[1]Department of Neurology, Yonsei University College of Medicine, Seoul, South Korea

[2]Department of Electronic Engineering, Hanyang University, Seoul, South Korea

[3]Department of Biomedical Engineering, Hanyang University, Seoul, South Korea

[4]Severance Biomedical Science Institute, Yonsei University College of Medicine, Seoul, South Korea

Correspondence
Phil Hyu Lee, Department of Neurology, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea.
Email: PHLEE@yuhs.ac

Jong-Min Lee, Department of Biomedical Engineering, Hanyang University, Sanhakgisulkwan #319, Wangsimni-ro, Seongdong-gu, Seoul 04763, Korea.
Email: ljm@hanyang.ac.kr

Funding information
Korean Healthy Industry Development Institute (KHIDI), Grant/Award Number: HU21C0053; National Research Foundation (NRF), Grant/Award Number: 2020M3E5D9080788

Abstract

Background and purpose: The aim was to investigate the neural correlates of impaired self-awareness of cognitive deficits (IACd) in non-demented patients with Parkinson's disease (PD).

Methods: This cross-sectional study enrolled 153 drug-naïve and non-demented PD patients who underwent brain magnetic resonance imaging, dopamine transporter (DAT) positron emission tomography, detailed neuropsychological testing, and the Cognitive Complaints Interview at baseline. Based on the presence of mild cognitive impairment and subjective cognitive complaints, patients were grouped into those with IACd (PD-IACd+, $n = 33$) and those with normal recognition of cognitive function ($n = 82$) or underestimation of cognitive function ($n = 38$). Cortical thickness, white matter (WM) integrity, DAT availability and cognitive function were compared between the groups.

Results: The prevalence of IACd was 21.6% in drug-naïve patients with PD. The PD-IACd+ group had a lower *z*-score in the Stroop color reading test than the other groups. Patients in the PD-IACd+ group had WM disintegrity, especially in the genu of the corpus callosum and anterior limb of the internal capsule, compared to those without IACd, whilst cortical thickness or striatal DAT availability was comparable regardless of the presence of IACd. Amongst patients with mild cognitive impairment, those with IACd had more severe WM disintegrity than those without IACd.

Conclusion: Structural connectivity between and from the frontal lobes is closely associated with self-awareness of cognitive deficits in PD. Evaluating frontal structural connectivity from the early stages of PD will be important in assessing the actual cognitive and daily life performance of patients with PD.

KEYWORDS
cognitive deficits, frontal lobe, Parkinson's disease, self-awareness, structural connectivity

INTRODUCTION

Patients with neurodegenerative diseases are often unaware of their cognitive, behavioral or functional impairment, which is called anosognosia [1]. The frequency of anosognosia in Alzheimer's disease (AD) was reported as up to 80% [2]. Patients with Huntington's disease (HD) show reduced awareness of physical and mental changes in themselves [3]. In Parkinson's disease (PD), impaired self-awareness of deficits can also be observed not only in motor symptoms but also in non-motor symptoms including cognition and

Han Soo Yoo and Hyeokjin Kwon contributed equally to this work.

is related to cognitive deficits [4,5]. Early identification of cognitive anosognosia greatly affects patients' disease course and caregiver burden because unawareness of their cognitive decline or medical condition may lead to dangerous circumstances via overestimation of their abilities in everyday life [6].

Imaging correlates of anosognosia have been studied mainly in AD. Cerebral hypometabolism including the hippocampus and cortical midline structures such as the orbitofrontal and posterior cingulate cortices and altered functional connectivity within these regions were observed in patients with anosognosia with amnestic mild cognitive impairment (MCI) [7] and AD [8]. Increasing anosognosia was also associated with atrophy in the medial temporal lobe in AD [9]. Low insight into motor dysfunction in HD was associated with striatal atrophy [10]. In PD, impaired self-awareness of motor disturbances was found to correlate with decreased glucose metabolism in the right inferior frontal gyrus [11]. However, no studies have evaluated the neural correlates of anosognosia of non-motor symptoms including cognition in PD.

The purpose of this study was to investigate the neural correlates of impaired self-awareness of cognitive deficits (IACd) in patients with PD without the administration of dopaminergic medications. Each patient's subjective cognitive complaints and objective cognitive decline were evaluated to define individuals with IACd. A comparative analysis of cortical thickness, diffusion tensor imaging (DTI) and striatal dopamine transporter (DAT) availability was then performed between non-demented and drug-naïve PD patients with and without IACd.

METHODS

Subjects

In this study, a cohort of 340 drug-naïve and non-demented patients with PD was used, the same cohort as in a previous study [5], who visited the movement disorders outpatient clinic at Severance Hospital, Yonsei University Health System, between May 2012 and November 2018. 153 patients were finally enrolled amongst the patients in this cohort who met the following inclusion criteria: (1) they had a PD diagnosis based on the clinical diagnostic criteria of the UK PD Society Brain Bank [12]; (2) they underwent detailed neuropsychological testing, the Cognitive Complaints Interview (CCI), three-dimensional volumetric brain magnetic resonance imaging (MRI) and ^{18}F *N*-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) positron emission tomography (PET) within 3 months; and (3) they had decreased DAT availability in the posterior putamen as interpreted by a nuclear medicine physician blinded to the clinical status of the patients. The exclusion criteria were as follows: (1) any evidence of motor, autonomic, oculomotor, and cognitive or neurobehavioral features indicative of atypical parkinsonism including multiple system atrophy, progressive supranuclear palsy and corticobasal degeneration [13]; (2) dementia at the time of baseline evaluation diagnosed on the basis of the Movement Disorder Society Task Force guideline [14]; (3) severe white matter (WM) hyperintensities [15], multiple lacunes in the basal ganglia, or hydrocephalus on MRI; (4) other neurological, psychiatric or metabolic illnesses; (5) history of drug use causing parkinsonian symptoms; and (6) poor image quality. Details of the enrollment of the study subjects are illustrated in Figure 1.

Parkinsonian motor severity was assessed during the drug-naïve state at the time of ^{18}F FP-CIT PET acquisition using the Unified Parkinson's Disease Rating Scale—part III. The self-rated Beck Depression Inventory (BDI) was used to assess depressive symptoms.

The Institutional Review Board of Yonsei University Severance Hospital approved this study, and written informed consent was obtained from all patients before enrollment.

Neuropsychological testing and diagnosis of cognitive status

A standard and comprehensive neuropsychological battery of tests called the Seoul Neuropsychological Screening Battery was performed for all subjects [16]. A detailed description of the neuropsychological battery and the diagnosis of level I possible PD-MCI is provided in Data S1.

Assessment of subjective cognitive complaints

The CCI was performed to evaluate subjective cognitive function before starting a comprehensive neuropsychological test [17], and a score over 3 was considered to reflect a significant complaint [18]. Of a total of 153 patients, 91 patients (59.5%) had no subjective cognitive complaints. A detailed description is provided in Data S2.

Grouping of subjects and the definition of IACd

Patients were grouped according to their objective cognitive status and CCI score (Figure 1). PD was defined with IACd (PD-IACd+, $n = 33$) when a patient had both CCI ≤3 (no subjective cognitive complaint) and MCI (objective cognitive decline); the remaining patients were considered to be without IACd (PD-IACd–, $n = 120$). Patients were further grouped in the PD-IACd– group into those with underestimation of cognitive function (PD-UCf, $n = 38$) when they had both CCI >3 and intact cognition and those with normal recognition of cognitive function (PD-NCf, $n = 82$) when they had both CCI ≤3 and intact cognition or both CCI >3 and MCI.

Magnetic resonance imaging and ^{18}F FP-CIT PET/computed tomography (CT) acquisition

Magnetic resonance imaging scans were acquired using a Philips 3.0 T scanner (Philips Achieva; Philips Medical System, Best, The Netherlands) with a SENSE head coil (SENSE factor = 2). ^{18}F FP-CIT PET/CT scans were obtained using a Discovery 600 system (General

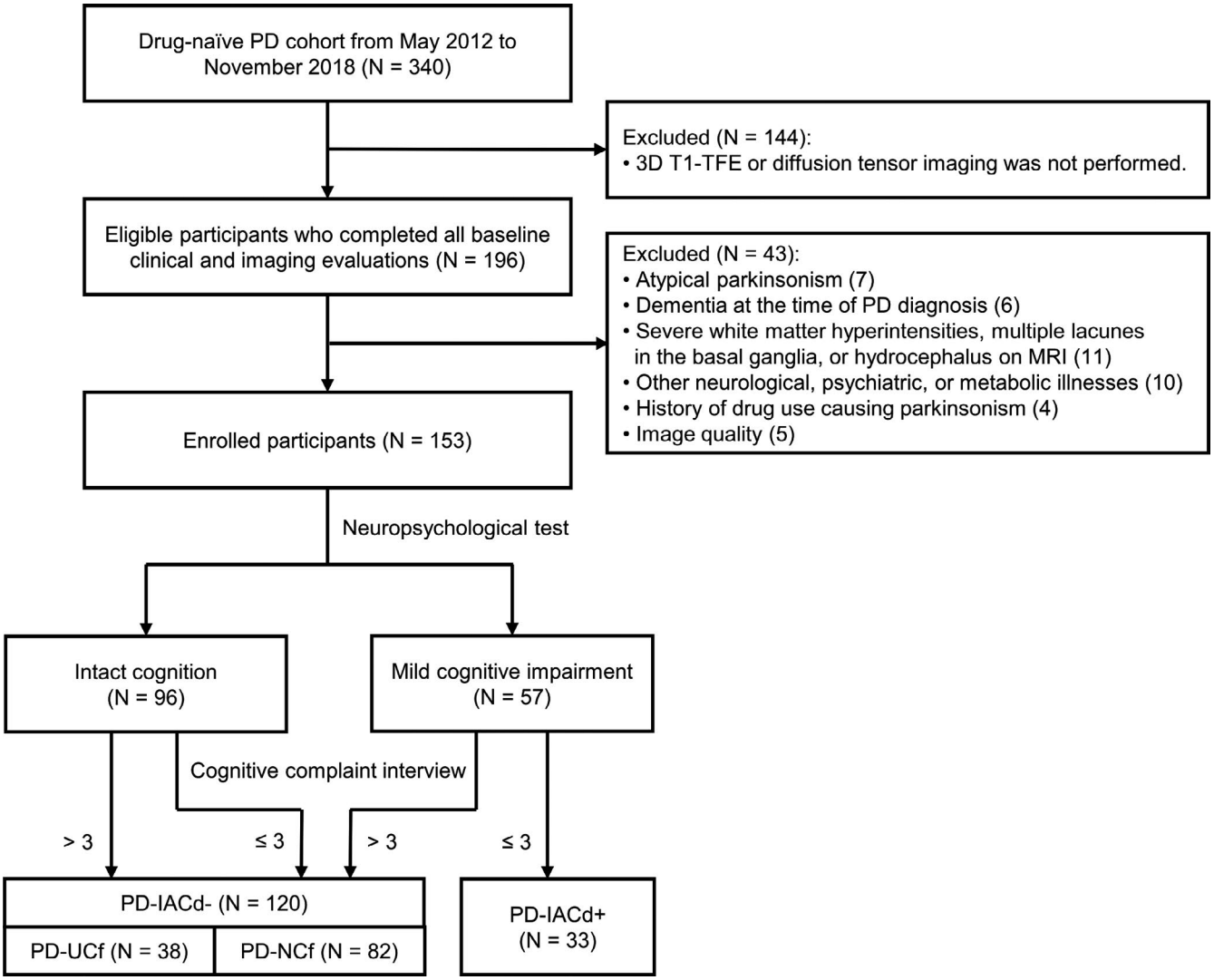

FIGURE 1 Flowchart of enrollment of the study subjects. PD, Parkinson's disease; ICAd, impaired self-awareness of cognitive deficits; UCf, underestimation of cognitive function; NCf, normal recognition of cognitive function

Electric Healthcare, Milwaukee, MI, USA). A detailed description is provided in Data S3.

Preprocessing of T1-weighted MRI data and analysis of cortical thickness

High-resolution T1-weighted MR images were processed using the CIVET pipeline (version 2.1.0) (http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET). Analysis of covariance at a vertex-wise level was performed to investigate whether the cortical thickness differed among the groups with SurfStat package (http://www.math.mcgill.ca/keith/surfstat). Age, sex, years of education, disease duration, and global composite z-score were used as covariates. All *p*-values were random-field theory (RFT)-corrected for multiple comparisons and the significance level was set to 0.05 after correction. A detailed description is provided in Data S4.

Preprocessing of DTI data and tract-based spatial statistics (TBSS) analysis

FMRIB's Software Library (http://www.fmrib.ox.ac.uk/fsl) was used to process the diffusion-weighted images. The dtifit tool was used to fit the diffusion tensor model and the diffusion scalar maps were calculated for fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity and radial diffusivity (RD) using the tensor eigenvalues (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/dtifit). For the TBSS analysis, voxel-wise non-parametric permutation tests of skeletonized images were performed to investigate group differences of FA, MD, axial diffusivity and RD. The number of permutations and the significance level were set to 5000 and 0.05 respectively after family-wise error rate correction for multiple comparisons using the threshold-free cluster enhancement. For consistency, the same covariates were used as in T1 MRI analysis. A detailed description is provided in Data S5.

Quantitation of the ^{18}F FP-CIT PET/CT images

Image processing was performed using MATLAB (The MathWorks Inc., Natick, MA, USA) software for Statistical Parametric Mapping 8 (SPM8) and ITK-SNAP (http://www.itksnap.org). Twelve volumes-of-interest of striatal subregions and one occipital volume-of-interest were drawn on the ^{18}F FP-CIT template, as described previously [19]. A detailed description is provided in Data S6.

Statistical analyses

Baseline demographic characteristics of the study subjects were analyzed using the independent *t* test and analysis of variance for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables as appropriate. To compare neuropsychological performance, analysis of covariance was performed using age, sex, years of education, disease duration and global composite *z*-score as covariates between the PD-IACd− and PD-IACd+ groups and between the PD-UCf, PD-NCf and PD-IACd+ groups. In particular, global composite *z*-scores were included as a covariate to adjust for general cognitive performance because the cognitive state of the PD groups was not equal. Bonferroni's method was used for post hoc subgroup analyses and for multiple comparisons of neuropsychological performance (13 tests). To investigate the association between IACd and WM integrity amongst patients with the same cognitive state, mean DTI values of the regions that showed significant differences in DTI values in all PD groups were compared between patients with PD-MCI with and without IACd. Analysis of covariance was performed with the same covariates and Bonferroni correction was applied for multiple comparisons. The data were analyzed using SPSS software version 24 (IBM Corporation, Armonk, NY, USA). $p < 0.05$ was considered significant.

RESULTS

Baseline demographic, clinical and cognitive characteristics of the study groups

Table 1 summarizes the baseline demographic characteristics and cognitive profile of the PD groups, which were similar to previous research. Of the 153 PD patients, 33 (21.6%) had IACd. The PD-IACd+ group had a lower total Korean version of the Mini-Mental State Examination score than those of the other groups. The PD-NCf group had higher CCI and BDI scores than the PD-IACd+ group and lower CCI and BDI scores than the PD-UCf group. Other clinical characteristics and intracranial volumes did not differ between the groups.

Regarding cognitive performance, the PD-IACd+ group had a significantly lower *z*-score for the digit span backward, Seoul Verbal Learning Test delayed recall and Stroop color reading test after controlling for age, sex, education, disease duration and global composite *z*-score. After Bonferroni's correction for multiple comparisons of the 13 neuropsychological items, the difference in the Stroop color reading test performance remained significant (Table S1). The clinical and neuropsychological characteristics of each patient in the PD-IACd+ group are presented in Table S2, and the comparison of frequencies of subjective reports and cognitive deficits by cognitive domain in the PD-IACd group are provided in Table S3. The PD-IACd+ group overestimated language problems and underestimated visuospatial, memory and frontal executive problems.

White matter integrity according to the presence of IACd

First, the WM integrity was compared between the PD-IACd− and PD-IACd+ groups (Figure 2a). The PD-IACd+ group had significantly lower FA values in the genu of the corpus callosum, bilateral anterior limb of the internal capsule and bilateral anterior corona radiata than the PD-IACd− group. In addition, the PD-IACd+ group had significantly higher axial diffusivity and RD values in extensive brain areas, including the genu and body of the corpus callosum, bilateral anterior limb of the internal capsule, right posterior limb of the internal capsule, and bilateral anterior and superior corona radiata, than the PD-IACd− group. Next, a comparative analysis of WM integrity was performed between the PD-IACd+, PD-NCf and PD-UCf groups (Figure 2b). The PD-IACd+ group had significantly lower FA and higher MD and RD values in the genu of the corpus callosum, bilateral anterior limb of the internal capsule and bilateral anterior corona radiata than the PD-UCf group. Additionally, the PD-IACd+ group had higher MD in the left posterior limb of the internal capsule and bilateral superior corona radiata. However, differences in WM integrity between the PD-UCf and PD-NCf or PD-NCf and PD-IACd+ groups did not reach statistical significance.

Cortical thickness and DAT availability according to the presence of IACd

There were no significant differences in either cortical thickness (Figure S1 for *T*-map) or in DAT availability in striatal subregions (Table 1) between the PD-IACd− and PD-IACd+ groups or between the PD-UCf, PD-NCf and PD-IACd+ groups.

Direct comparison of mean values of WM integrity between PD-MCI with and without IACd

Mean values of WM integrity between patients with PD-MCI with and without IACd were also compared to investigate the association between IACd and WM integrity amongst patients with the same cognitive state (Figure 3). Patients with PD-MCI with IACd had significantly lower mean FA values in the genu of the corpus callosum and anterior limb of the internal capsule and higher RD values in the genu of the corpus callosum than those without IACd.

TABLE 1 Baseline demographic and clinical characteristics of the study subjects

	PD-IACd					
	All	PD-UCf	PD-NCf	PD-IACd+	*p* value*	*p* value**
Number (%)	120 (78.4)	38 (24.8)	82 (53.6)	33 (21.6)		
Age at onset, years	64.60 ± 9.45	64.58 ± 9.64	64.60 ± 9.41	66.43 ± 8.78	0.318	0.609
Sex, male (%)	61 (50.8)	20 (52.6)	42 (50.6)	20 (60.6)	0.319	0.620
Education, years	10.66 ± 4.37	9.71 ± 4.00	11.10 ± 4.49	10.50 ± 5.13	0.859	0.293
Disease duration, years	1.66 ± 1.68	1.17 ± 0.92	1.89 ± 1.89	1.50 ± 1.09	0.600	0.055
UPDRS motor score	20.20 ± 8.88	20.58 ± 10.13	20.02 ± 8.30	22.45 ± 8.45	0.194	0.410
Total K-MMSE score	27.33 ± 2.19	27.50 ± 1.66	27.26 ± 2.41	26.21 ± 2.50	0.013	0.039[b,c]
CCI	3.58 ± 2.47	5.63 ± 1.55	2.63 ± 2.23	1.33 ± 1.05	<0.001	<0.001[a,b,c]
BDI	13.03 ± 8.82	15.49 ± 6.83	11.93 ± 9.42	8.30 ± 8.23	0.006	0.003[a,b,c]
Vascular risk factor						
Hypertension	55 (45.8)	18 (47.4)	38 (45.8)	14 (42.4)	0.727	0.913
Diabetes mellitus	22 (18.3)	7 (18.4)	15 (18.1)	10 (30.3)	0.134	0.314
Hyperlipidemia	26 (21.7)	8 (21.1)	18 (21.7)	10 (30.3)	0.300	0.568
Cardiac disease	11 (9.2)	6 (15.8)	5 (6.0)	2 (6.1)	0.571	0.172
Intracranial volume, mm^3	1009.45 ± 103.18	1005.61 ± 88.23	1011.23 ± 109.88	1034.20 ± 140.04	0.288	0.525
DAT availability						
Anterior caudate	2.43 ± 0.64	2.32 ± 0.61	2.48 ± 0.65	2.26 ± 0.71	0.242	0.257
Posterior caudate	1.67 ± 0.55	1.60 ± 0.51	1.71 ± 0.57	1.57 ± 0.51	0.379	0.407
Anterior putamen	2.49 ± 0.61	2.46 ± 0.52	2.50 ± 0.65	2.39 ± 0.74	0.499	0.754
Posterior putamen	1.64 ± 0.48	1.69 ± 0.46	1.61 ± 0.49	1.63 ± 0.68	0.953	0.793
Ventral putamen	1.69 ± 0.41	1.72 ± 0.41	1.68 ± 0.42	1.66 ± 0.52	0.764	0.876
Ventral striatum	2.15 ± 0.50	2.10 ± 0.41	2.18 ± 0.53	2.02 ± 0.52	0.227	0.365

Note: Values are expressed as mean ± standard deviation or number (percentage) if appropriate.

There is a significant difference in the comparison between [a]PD-UCf and PD-NCf, between [b]PD-UCf and PD-IACd+ groups and between [c]PD-NCf and PD-IACd+ groups.

Abbreviations: BDI, Beck Depression Inventory; CCI, Cognitive Complaints Interview; DAT, dopamine transporter; IACd, impaired self-awareness of cognitive deficit; K-MMSE, Korean version of the Mini-Mental State Examination; NCf, normal recognition of cognitive function; PD, Parkinson's disease; UCf, underestimation of cognitive function; UPDRS, Unified Parkinson's Disease Rating Scale.

*Comparison between the PD-IACd− and PD-IACd+groups.; **Comparison among the PD-UCf, PD-NCf, and PD-IACd+groups.

DISCUSSION

In this study, the neural correlates of IACd in non-demented and drug-naïve patients with PD were investigated. The major findings were as follows. First, the prevalence of IACd in PD was 21.6% and PD patients with IACd had lower cognitive performance, especially in the Stroop color reading item. Secondly, PD patients with IACd had WM disintegrity, especially in the genu of the corpus callosum and anterior limb of the internal capsule, compared to those without IACd, whilst cortical thickness or striatal DAT availability was comparable regardless of the presence of IACd. Thirdly, amongst patients with PD-MCI, those with IACd had more severe WM disintegrity than those without IACd. Taken together, it was demonstrated that IACd in PD is associated with impaired frontal structural connectivity, such as in the genu of the corpus callosum as the commissural fibers and the anterior limb of the internal capsule as the projection fibers.

Cognitive impairment, one of the most common and significant non-motor symptoms in PD, is often underestimated by patients themselves. Our study showed that approximately one-fifth of patients with PD not taking any anti-parkinsonian medication at the time of PD diagnosis were not able to recognize their cognitive impairment correctly. Similar to our study result, others have shown that PD patients overestimated their cognitive abilities by 15%–24% [20] and that 16% of patients with multi-domain PD-MCI had anosognosia for cognitive and behavioral symptoms [4]. Importantly, IACd is associated with cognitive dysfunction. It was demonstrated that the presence of IACd was closely related to poor cognitive dysfunction, especially in the Stroop color reading test, which assesses one's ability to inhibit cognitive interference and reflects frontal executive function, working memory, cognitive flexibility and processing speed [21]. In line with our study, frontal executive dysfunction has commonly been reported to be associated significantly with anosognosia in both PD [4,22] and AD [23]. Just as in patients with PD,

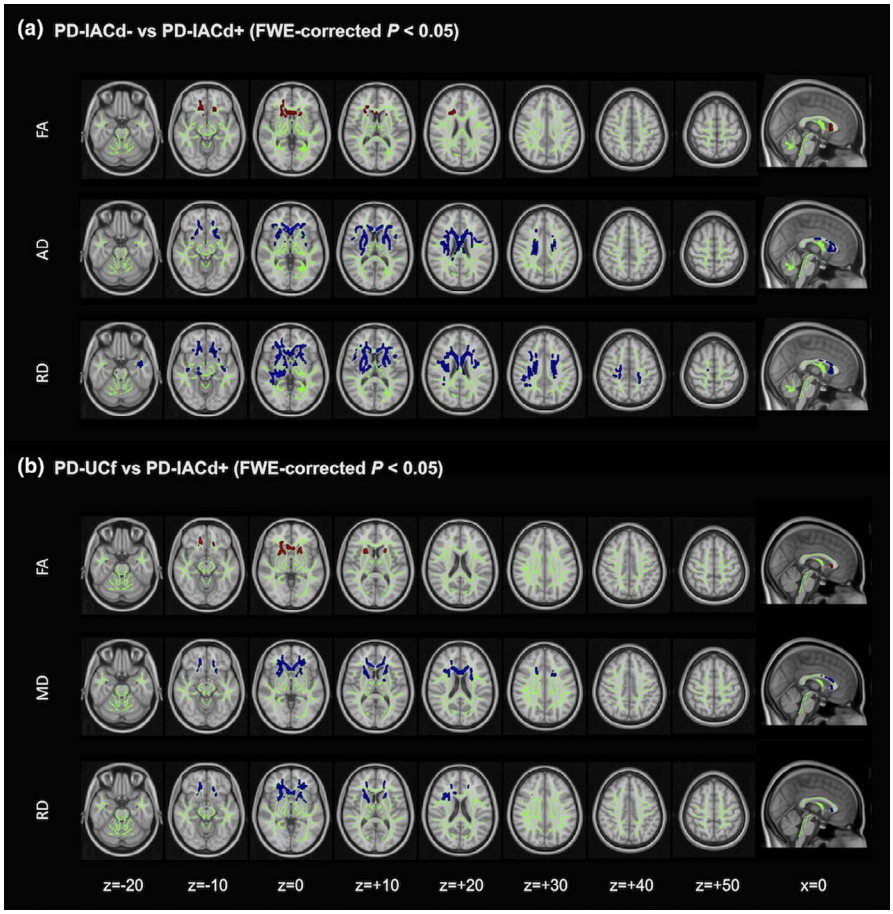

FIGURE 2 TBSS maps of the comparison of white matter integrity between the groups. (a) Comparisons between the PD-IACd– and PD-IACd+ groups and (b) between the PD-UCf, PD-NC and PD-IACd+ groups (FWE-corrected $p < 0.05$). Red to yellow color on the corrected *p*-map indicates brain regions where the latter group had a lower value than the former group, whilst blue color on the corrected *p*-map indicates brain regions where the latter group had a higher value than the former group. (b) Only the TBSS map of the subgroup comparison is presented which shows a significant difference after Bonferroni's correction. The brain images are displayed following neurological convention. TBSS, track-based spatial statistics; ICAd, impaired self-awareness of cognitive deficit; UCf, underestimation of cognitive function; NCf, normal recognition of cognitive function; PD, Parkinson's disease, FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; FWE, family-wise error rate [Colour figure can be viewed at wileyonlinelibrary.com]

those with HD, another neurodegenerative, basal ganglia disorder, also show reduced awareness in both motor and cognitive symptoms [3]. HD patients with high anosognosia showed lower performance in the Wisconsin Card Sorting Test than those with low anosognosia, implicating involvement of a prefrontal pathway [24]. It can be inferred from these results that frontal executive dysfunction may be a contributor to impaired perception of one's cognitive function and that clinicians or caregivers should pay attention to patients' objective cognitive abilities even if they do not complain of cognitive dysfunction.

Interestingly, in line with a previous study [25], PD patients with IACd tended to underestimate visuospatial, memory and frontal executive dysfunction and to overestimate language dysfunction, suggesting that IACd could be cognitive-domain-specific. It is known that patients with PD exhibit characteristic cognitive decline in attentional, executive, memory and visuospatial domains, whereas language function remains generally intact. Therefore, it seems that PD patients likely underestimate deficits in cognitive function, which is commonly impaired in PD, and overestimate deficits in cognitive function, which is relatively preserved. At this point, it is not known why PD patients with cognitive decline exhibit contradictory subjective perceptions depending on whether they have objective cognitive impairment. Moreover, our findings require cautious interpretation because the items in the CCI neither clearly cover all different cognitive domains nor can be assigned to specific cognitive domains. Further studies with a large sample of PD patients with cognitive impairment that employ the use of cognitive-domain-specific evaluations of subjective cognitive complaints are required to obtain insights into specific cognitive dysfunction.

In the present study, it was found for the first time that IACd in PD was associated with frontal WM disintegrity, especially involving the genu of the corpus callosum and anterior limb of the internal capsule. The corpus callosum is a bundle of commissural fibers that connect the two cerebral hemispheres and is essential for communication between the two hemispheres; its genu part connects the lateral and medial surfaces of the frontal lobes. The anterior limb of

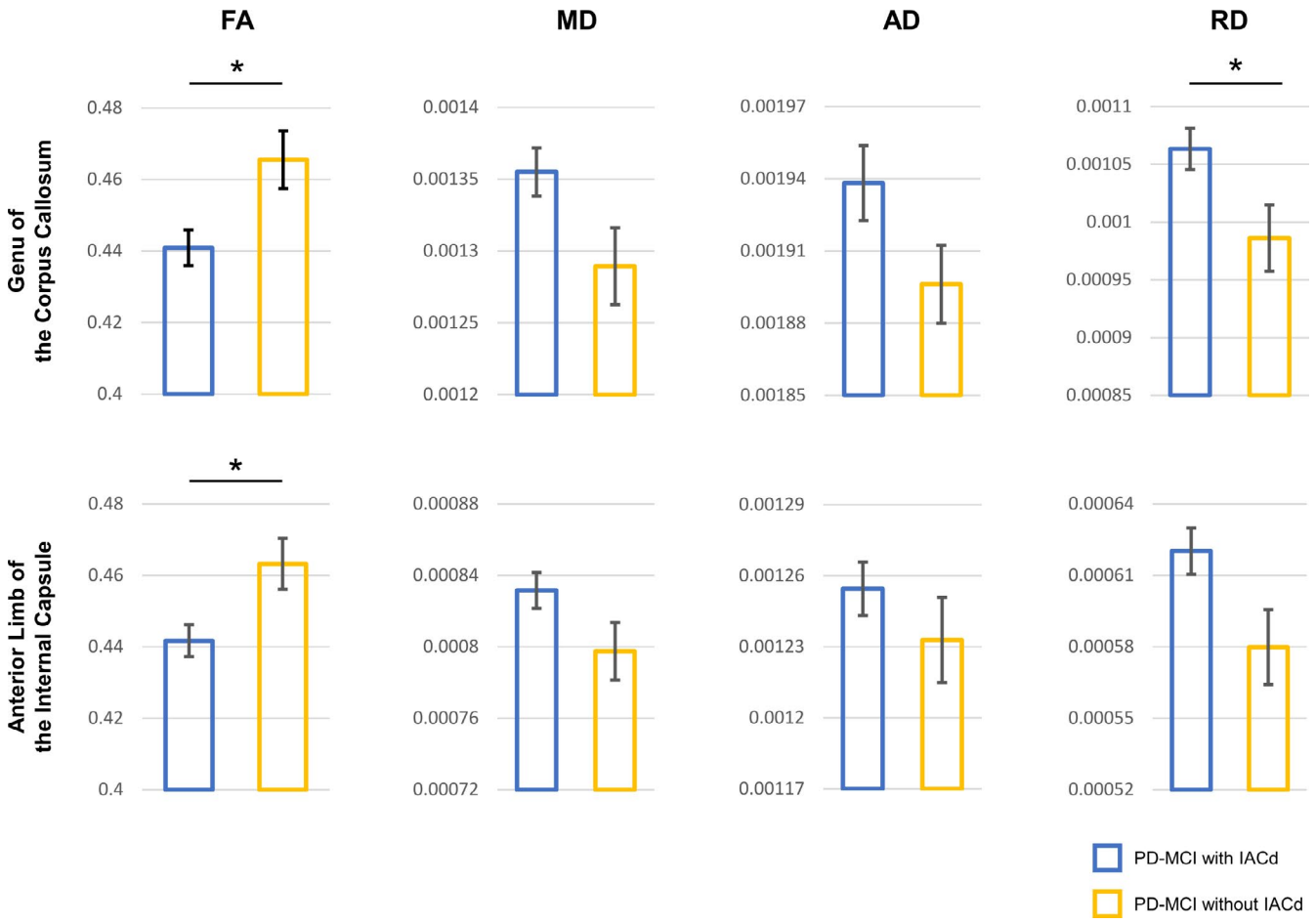

FIGURE 3 Bar graphs of group comparisons of mean white matter integrity according to the presence of impaired self-awareness of cognitive deficits in Parkinson's disease with mild cognitive impairment. An asterisk indicates significant differences between the two groups. AD, axial diffusivity; FA, fractional anisotropy; IACd, impaired self-awareness of cognitive deficits; MCI, mild cognitive impairment; MD, mean diffusivity; PD, Parkinson's disease; RD, radial diffusivity [Colour figure can be viewed at wileyonlinelibrary.com]

the internal capsule contains fibers of the anterior thalamic radiation, which connect the thalamus with the prefrontal cortex [26]. In AD, imaging studies have demonstrated that anosognosia was associated with hypometabolism in the ventromedial and orbitofrontal regions [8,9,27]. Hypometabolism in the orbitofrontal cortex may prevent patients from updating their qualitative judgment associated with the impaired cognitive abilities [9]. Another study proposed that dorsal medial prefrontal cortex dysfunction results in a deficit in third-person perspective taking, thereby leading to impaired cognitive awareness [28]. In patients with PD, FA values in the genu of the corpus callosum were reported to be associated with general cognition and dementia [29], and executive function directly correlated with FA and inversely correlated with MD in the anterior limb of the internal capsule and genu of the corpus callosum [30]. Additionally, HD shows more deficient self-awareness of symptoms than PD [31,32], probably resulting from more widespread neurodegeneration encompassing the prefrontal cortex, corpus callosum, and orbitostriatal WM tracts [3]. These studies suggest that impaired communication between bilateral frontal lobes and between frontal cortex and thalamus may not only contribute to cognitive dysfunction but also play a crucial role in recognizing one's cognitive ability correctly. Thus, impaired frontal connectivity can be a useful biomarker for IACd from the early stages of PD.

Depletion of dopamine neurotransmitter in the nigrostriatal pathway is a pathognomonic finding in PD, and dopamine depletion in the caudate is known to be correlated with cognitive dysfunction, mainly in frontal executive performance [33]. In this study, however, it was found that dysfunction of dopamine neurotransmitters was not related to proper recognition of cognitive impairment in patients with PD. In addition, our data showed that frontal atrophy, an important marker of cognitive decline and conversion to dementia in PD [34], was not associated with IACd in PD. This is probably attributable to the recruitment of patients with early stage PD. Although local cortical atrophy can lead to cognitive dysfunction related to the area, our results indicated that frontal connectivity is more important for recognizing cognitive decline than cortical atrophy.

Awareness is composed of four levels: sensory registration, performance monitoring, evaluative judgment and metarepresentation [35]. Given previous studies on AD, medial temporal dysfunction may lead to impairments in the comparison between objective cognitive impairment and subjective cognitive complaint, parieto-temporal dysfunction may be associated with deficits in sensory registration

and processing of self-significant information, and the medial prefrontal cortex may participate in self-monitoring and judgment of one's impaired cognitive abilities [9]. Since these regions are typically areas of atrophy and hypometabolism in AD [36,37], dysfunction in any of these regions can contribute to anosognosia in patients with AD. Meanwhile, patients with PD are characterized by frontal executive dysfunction and frontal atrophy [38,39]. Therefore, frontal lobe dysfunction may interfere with self-monitoring and judging mismatch between incoming information and stored representations, which may be a major mechanism of IACd in PD.

This study has several limitations. First, unlike previous studies that used questionnaires to evaluate discrepancies in performance ratings between patients and clinicians/caregivers, patients' IACd was assessed by comparing objective cognitive decline with subjective cognitive complaints. This strategy can be influenced by patient's general and emotional conditions. However, it could be difficult to detect subtle IACd through an interview with clinician or caregiver because cognitive impairment in the patients enrolled in this study was not as severe as that in patients with dementia. To generalize the study results, further studies using typical questionnaires for anosognosia to investigate the correlation between its quantitative scores and imaging parameters are necessary. Secondly, anosognosia was not evaluated in terms of motor symptoms, and no conclusion can be drawn about whether frontal lobe dysfunction is a neural substrate specific to IACd or a structure related to impaired self-awareness in general deficits. Future studies investigating the neural substrates of anosognosia of motor deficits or other non-motor symptoms are necessary to reveal the granular mechanisms of self-awareness. Thirdly, only one test was assigned to evaluate language and visuospatial functions, respectively, and the Rey–Osterrieth Complex Figure test can be used to evaluate not only visuospatial function but also memory and executive function [40]. Also, the Stroop color reading test assesses only certain aspects of frontal executive function. Performing at least two tests covering various aspects of cognitive function in each domain would be necessary to accurately evaluate domain-specific cognitive function. Fourthly, functional imaging studies were not performed using fluorodeoxyglucose PET or functional MRI, which may show different patterns of neural correlates associated with self-awareness.

In conclusion, our data suggest that structural connectivity between and from the frontal lobes is closely associated with self-awareness of cognitive deficits in PD. Evaluating frontal structural connectivity from the early stages of PD will be important in assessing the actual cognitive and daily life performance of patients with PD.

ACKNOWLEDGEMENTS

This work was supported by a grant from the Korea Health Technology R&D Project through the Korean Healthy Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number HU21C0053), awarded to Phil Hyu Lee and the Bio and Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (grant number 2020M3E5D9080788) awarded to Jong-Min Lee.

CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

Han Soo Yoo: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); writing—original draft (equal); writing—review and editing (equal). Hyeokjin Kwon: Conceptualization (equal); formal analysis (equal); investigation (equal); methodology (equal); resources (equal); software (equal); writing—original draft (equal); writing—review and editing (equal). Seok Jong Chung: Data curation (equal); formal analysis (equal); methodology (equal); writing—review and editing (equal). Young H. Sohn: Project administration (equal); resources (equal); supervision (equal); writing—review and editing (equal). Jong Min Lee: Methodology (equal); project administration (equal); software (equal); supervision (equal); validation (equal); visualization (equal); writing—review and editing (equal). Phil Hyu Lee: Conceptualization (equal); investigation (equal); project administration (equal); resources (equal); supervision (equal); validation (equal); writing—review and editing (equal).

DATA AVAILABILITY STATEMENT

For the purpose of replicating the procedures and results, any qualified investigator can request anonymized data after ethics clearance and approval from all authors.

ORCID

Han Soo Yoo https://orcid.org/0000-0001-7846-6271
Seok Jong Chung https://orcid.org/0000-0001-6086-3199

REFERENCES

1. Selnes OA. Awareness of deficit after brain injury. Clinical and theoretical issues. *Electroencephalogr Clin Neurophysiol*. 1994;91:315-316.
2. Starkstein SE. Anosognosia in Alzheimer's disease: diagnosis, frequency, mechanism and clinical correlates. *Cortex*. 2014;61:64-73.
3. Sitek EJ, Thompson JC, Craufurd D, Snowden JS. Unawareness of deficits in Huntington's disease. *J Huntingtons Dis*. 2014;3:125-135.
4. Orfei MD, Assogna F, Pellicano C, et al. Anosognosia for cognitive and behavioral symptoms in Parkinson's disease with mild dementia and mild cognitive impairment: frequency and neuropsychological/neuropsychiatric correlates. *Parkinsonism Relat Disord*. 2018;54:62-67.
5. Yoo HS, Chung SJ, Lee YH, Ye BS, Sohn YH, Lee PH. Cognitive anosognosia is associated with frontal dysfunction and lower depression in Parkinson's disease. *Eur J Neurol*. 2020;27:951-958.
6. Turró-Garriga O, Garre-Olmo J, Reñé-Ramírez R, Calvó-Perxas L, Gascón-Bayarri J, Conde-Sala J-L. Consequences of anosognosia on the cost of caregivers' care in Alzheimer's disease. *J Alzheimers Dis*. 2016;54:1551-1560.
7. Vannini P, Hanseeuw B, Munro CE, et al. Anosognosia for memory deficits in mild cognitive impairment: insight into the neural mechanism using functional and molecular imaging. *Neuroimage Clin*. 2017;15:408-414.

8. Perrotin A, Desgranges B, Landeau B, et al. Anosognosia in Alzheimer disease: disconnection between memory and self-related brain networks. *Ann Neurol*. 2015;78:477-486.
9. Salmon E, Perani D, Herholz K, et al. Neural correlates of anosognosia for cognitive impairment in Alzheimer's disease. *Hum Brain Mapp*. 2006;27:588-597.
10. Justo D, Charles P, Daunizeau J, et al. Is non-recognition of choreic movements in Huntington disease always pathological? *Neuropsychologia*. 2013;51:748-759.
11. Maier F, Williamson KL, Tahmasian M, et al. Behavioural and neuroimaging correlates of impaired self-awareness of hypo- and hyperkinesia in Parkinson's disease. *Cortex*. 2016;82:35-47.
12. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1988;51:745-752.
13. Wenning GK, Litvan I, Tolosa E. Milestones in atypical and secondary parkinsonisms. *Mov Disord*. 2011;26:1083-1095.
14. Dubois B, Burn D, Goetz C, et al. Diagnostic procedures for Parkinson's disease dementia: recommendations from the Movement Disorder Society Task Force. *Mov Disord*. 2007;22:2314-2324.
15. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol*. 1987;149:351-356.
16. Ahn HJ, Chin J, Park A, et al. Seoul Neuropsychological Screening Battery—dementia version (SNSB-D): a useful tool for assessing and monitoring cognitive impairments in dementia patients. *J Korean Med Sci*. 2010;25:1071-1076.
17. Dujardin K, Duhamel A, Delliaux M, Thomas-Anterion C, Destee A, Defebvre L. Cognitive complaints in Parkinson's disease: its relationship with objective cognitive decline. *J Neurol*. 2010;257:79-84.
18. Thomas-Antérion C, Honoré-Masson S, Laurent B. The cognitive complaint interview (CCI). *Psychogeriatrics*. 2006;6:S18-S22.
19. Oh M, Kim JS, Kim JY, et al. Subregional patterns of preferential striatal dopamine transporter loss differ in Parkinson disease, progressive supranuclear palsy, and multiple-system atrophy. *J Nucl Med*. 2012;53:399-406.
20. McKie K. *Awareness of cognitive abilities in people with Parkinson's disease*. D Clin Psy Thesis, University of Glasgow; 2015.
21. Scarpina F, Tagini S. The Stroop color and word test. *Front Psychol*. 2017;8:557.
22. Kudlicka A, Clare L, Hindle JV. Awareness of executive deficits in people with Parkinson's disease. *J Int Neuropsychol Soc*. 2013;19:559-570.
23. Michon A, Deweer B, Pillon B, Agid Y, Dubois B. Relation of anosognosia to frontal lobe dysfunction in Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 1994;57:805-809.
24. Deckel AW, Morrison D. Evidence of a neurologically based "denial of illness" in patients with Huntington's disease. *Arch Clin Neuropsychol*. 1996;11:295-302.
25. Copeland JN, Lieberman A, Oravivattanakul S, Troster AI. Accuracy of patient and care partner identification of cognitive impairments in Parkinson's disease–mild cognitive impairment. *Mov Disord*. 2016;31:693-698.
26. Safadi Z, Grisot G, Jbabdi S, et al. Functional segmentation of the anterior limb of the internal capsule: linking white matter abnormalities to specific connections. *J Neurosci*. 2018;38:2106-2117.
27. Rosen HJ. Anosognosia in neurodegenerative disease. *Neurocase*. 2011;17:231-241.
28. Jedidi H, Feyers D, Collette F, et al. Dorsomedial prefrontal metabolism and unawareness of current characteristics of personality traits in Alzheimer's disease. *Soc Cogn Affect Neurosci*. 2014;9:1458-1463.
29. Kamagata K, Motoi Y, Tomiyama H, et al. Relationship between cognitive impairment and white-matter alteration in Parkinson's disease with dementia: tract-based spatial statistics and tract-specific analysis. *Eur Radiol*. 2013;23:1946-1955.
30. Zheng Z, Shemmassian S, Wijekoon C, Kim W, Bookheimer SY, Pouratian N. DTI correlates of distinct cognitive impairments in Parkinson's disease. *Hum Brain Mapp*. 2014;35:1325-1333.
31. Sitek EJ, Sołtan W, Wieczorek D, et al. Self-awareness of motor dysfunction in patients with Huntington's disease in comparison to Parkinson's disease and cervical dystonia. *J Int Neuropsychol Soc*. 2011;17:788-795.
32. Sitek EJ, Sołtan W, Wieczorek D, et al. Self-awareness of executive dysfunction in Huntington's disease: comparison with Parkinson's disease and cervical dystonia. *Psychiatry Clin Neurosci*. 2013;67:59-62.
33. Rinne JO, Portin R, Ruottinen H, et al. Cognitive impairment and the brain dopaminergic system in Parkinson disease: [18F] fluorodopa positron emission tomographic study. *Arch Neurol*. 2000;57:470-475.
34. Chung SJ, Yoo HS, Lee YH, et al. Frontal atrophy as a marker for dementia conversion in Parkinson's disease with mild cognitive impairment. *Hum Brain Mapp*. 2019;40:3784-3794.
35. Clare L, Marková IS, Roth I, Morris RG. Awareness in Alzheimer's disease and associated dementias: theoretical framework and clinical implications. *Aging Ment Health*. 2011;15:936-944.
36. Dickerson BC, Bakkour A, Salat DH, et al. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cereb Cortex*. 2009;19:497-510.
37. Perovnik M, Rus T, Tomše P, et al. Identification and validation of Alzheimer's disease-related metabolic pattern in patients with pathologically confirmed Alzheimer's disease. *Alzheimers Dement*. 2020;16:e042629.
38. Double KL, Halliday GM, McRitchie DA, Reid WG, Hely MA, Morris JG. Regional brain atrophy in idiopathic Parkinson's disease and diffuse Lewy body disease. *Dementia*. 1996;7:304-313.
39. Taylor AE, Saint-Cyr JA, Lang AE. Frontal lobe dysfunction in Parkinson's disease. The cortical focus of neostriatal outflow. *Brain*. 1986;109(Pt 5):845-883.
40. Shin M-S, Park S-Y, Park S-R, Seol S-H, Kwon JS. Clinical and empirical applications of the Rey–Osterrieth Complex Figure Test. *Nat Protoc*. 2006;1:892-899.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Appendix S1

How to cite this article: Yoo HS, Kwon H, Chung SJ, Sohn YH, Lee J-M, Lee PH. Neural correlates of self-awareness of cognitive deficits in non-demented patients with Parkinson's disease. *Eur J Neurol*. 2021;28:4022–4030. https://doi.org/10.1111/ene.15095