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Altered Nigrostriatal and Nigrocortical Functional Connectivity in Rapid Eye Movement Sleep Behavior Disorder

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Study Objectives: Rapid eye movement sleep behavior disorder (RBD) is a condition closely associated with Parkinson disease (PD). RBD is a sleep disturbance that frequently manifests early in the development of PD, likely reflecting disruption in normal functioning of anatomical areas affected by neurodegenerative processes. Although specific neuropathological aspects shared by RBD and PD have yet to be fully documented, further characterization is critical to discovering reliable biomarkers that predict PD onset. In the current study, we tested the hypothesis of altered functional connections of the substantia nigra (SN) in patients in whom RBD was diagnosed.

Design: Between-groups, single time point imaging.

Setting: UTHSC-H 3 telsa MRI center.

Participants: Ten patients with RBD, 11 patients with PD, and 10 age-matched controls.

Interventions: NA.

Measurements and Results: We measured correlations of SN time series using resting state blood oxygen level-dependent functional magnetic resonance imaging (BOLD-fMRI) in patients with idiopathic RBD who were at risk for developing PD, patients in whom PD was diagnosed, and age-matched controls. Using voxelwise analysis of variance, different correlations ($P < 0.01$, whole-brain corrected) between left SN and left putamen were found in patients with RBD compared with controls and patients with PD. SN correlations with right cuneus/precuneus and superior occipital gyrus were significantly different for patients with RBD compared with both controls and patients with PD.

Conclusions: The results suggest that altered nigrostriatal and nigrocortical connectivity characterizes rapid eye movement sleep behavior disorder before onset of obvious motor impairment. The functional changes are discussed in the context of degeneration in dopaminergic and cognition-related networks.

Keywords: Parkinson disease, putamen, REM sleep behavior disorder, resting state fMRI, substantia nigra

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INTRODUCTION

Rapid eye movement sleep behavior disorder (RBD) is a condition closely associated with Parkinson disease (PD) and frequently arises as an early manifestation in PD.[1,2] Most patients (~65%) with idiopathic RBD develop PD or other progressive neurodegenerative parkinsonian syndromes years after diagnosis.[3,4] RBD may therefore be a subclinical indicator of a neurodegenerative condition,[3] with altered striatal dopaminergic innervation[5,6] and evidence of striatal volumetric differences.[7] Together these observations suggest that some aspects of RBD reflect changes in the normal functioning of anatomical areas affected by the same, or similar, neurodegenerative process that results in the later development of PD. Identification of PD biomarkers, especially in the early premotor stages of neurodegeneration, would help to guide neuroprotective treatments before severe motor impairment occurs. The identification of early neuropathological changes in patients with RBD that are shared by patients with PD is therefore an important research objective.

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Structural imaging[7] and diffusion-weighted magnetic resonance imaging (MRI) measures of the basal ganglia[8] have shown promise for characterizing early neuroanatomical correlates of PD. Spatially correlated spontaneous fluctuations in the blood oxygen level-dependent functional magnetic resonance imaging (BOLD-fMRI) signal[9] represent another promising tool. Several studies have investigated these functional signals to reveal functional networks in healthy individuals.[10,11] The similarity of temporal changes in BOLD-fMRI, which is an indirect measure of neuronal activity, between different brain regions is hypothesized to reflect functional connectivity, or the degree that activity between brain areas is coordinated. Functional connectivity is potentially useful clinically and predictive of, for example, recovery after stroke,[12] and suggests that BOLD-fMRI resting state connectivity is a potentially valuable marker and predictor of disease states. Resting state BOLD-fMRI is also promising for its safety and availability in clinical settings and because it does not require task performance, which often varies among patients. A recent functional connectivity study demonstrated mapping of individual functional basal ganglia circuits, which holds tremendous promise for studying PD pathophysiology.[13] Remapping of corticostriatal circuits in large samples of patients with PD, consistent with the hypothesis that dopamine depletion has widespread effects on brain networks, particularly connections with putamen, has also been demonstrated.[14,15] Yet, resting state fMRI has not yet been used to investigate the functional connectivity of the nigrostriatal or

Table 1—Demographics and statistical significance of behavioral and clinical measures among control, PD, and patients with RBD.

Patient group (means ± SEM)	Control (n = 10)	RBD (n = 10)	PD (n = 11)	P value
Age (range, years)	57 ± 2.4 (37-64)	57 ± 2.7 (37-65)	62 ± 2.5 (47-74)	ns
Sex	4 m, 6 f	6 m, 4 f	7 m, 4 f	
Handedness	1 left	1 left	1 left	
Hoehn and Yahr (0-5)	0	0.4 ± 0.16 (0-1)	1.86 ± 0.32 (1-3.5)	a*** b**
Sleep study (PSG)	RBD (0); RLS (1)	RBD(10); RBD & RLS(1)	RBD (10); normal (1)	
Montreal Cognitive Assessment (MoCA)	28.9 ± 0.6 (25-30)	27.8 ± 0.68 (23-30)	28 ± 0.77 (23-30)	ns
UPDRS-total I-IV subscales	3.6 ± 1.2 (0-8)	12 ± 1.99 (3-22)	33 ± 5.5 (9-65)	a***
Most affected side (symptoms)	na	na	8 Right, 3 Left	

a = C vs. PD, b = PD vs. RBD. **P < 0.01, ***P < 0.001. Age, Hoehn and Yahr, Unified Parkinson Disease Rating Scale (UPDRS)-total and MoCA compared with Kruskal-Wallis analysis of variance. PD, Parkinson disease; PSG, polysomnography; RBD, rapid eye movement sleep behavior disorder; SEM, standard error of the mean

nigrocortical pathways in patients with idiopathic RBD who are presymptomatic but at risk for developing PD, and in whom altered functional connectivity may exist.

In the current study, we used resting state BOLD-fMRI to test the primary hypothesis that functional coordination between substantia nigra (SN) and striatum is compromised in patients with RBD and those with early to moderate PD. Neuroanatomical studies document the existence of an excitatory dopaminergic pathway between SN and striatum,[16] which degenerates as PD progresses.[17] In our study, in most patients with PD, the right side of their body was most affected, and it has recently been shown with nuclear imaging that there is left hemispheric predominance of nigrostriatal dysfunction in PD.[18] Imaging of nigrostriatal function with resting state fMRI was also demonstrated recently in young volunteers.[19] Here, we specifically predicted correlation strength between SN and striatum will be decreased relative to age-matched controls in patients diagnosed by dream enactment history, neurological examination, and videopolysomnography as having idiopathic rapid eye movement sleep behavior disorder (RBD),[20] and that functional connectivity between SN and striatum would also be reduced in patients with PD. In order to fully understand the differential SN connectivity patterns that distinguish RBD, a secondary objective was to identify other regions, including cortex, that differ among patients with RBD, controls, and those with PD. To evaluate both of these hypotheses, we used voxel-wise analysis of variance (ANOVA) of resting- state SN correlations maps followed by a whole-brain multiple comparisons correction.

METHODS

Participants

Thirty-one participants provided informed consent and were enrolled into a study approved by our local Institutional Review Board and in accordance with the Declaration of Helsinki. Participants were recruited from the sleep clinic or neurology clinic, or referred to our study from its entry at www.clinicaltrials.gov. Each was assigned to one of three groups according to inclusion criteria detailed in the next paragraphs and in Table 1. Included are 10 age-matched control subjects, 10 patients with RBD, and 11 patients with PD. Inclusion criteria included men and women age 30-85 y old who did not have an unstable medical or psychiatric condition, renal or liver failure, or significant dementia and met criteria for one of the study groups including an early-to-moderate PD group, an idiopathic RBD group, and a control group. A diagnosis in patients with PD is made based on Gelb et al.'s diagnostic criteria for Parkinson disease[21] and the United Kingdom Brain Bank criteria of bradykinesia plus one or more cardinal motor symptoms,[22] including unilateral rest tremor, rigidity, or mild gait impairment and postural instability. Patients with parkinsonian symptoms due to atypical parkinsonism, vascular PD, or medicine-/toxin-induced parkinsonism were excluded. To exclude advanced disease, we used the Hoehn and Yahr disability scale[23] with a cutoff of ≤ 3.5 in the off medicine state. The RBD group diagnostic criteria is based on the American Academy of Sleep Medicine[20] criteria to include the presence of rapid eye movement (REM) sleep without atonia and at least one of the following: sleep related injurious, potentially injurious, or disruptive behaviors by history; abnormal REM sleep behaviors documented during videopolysomnography and the absence of electroencephalographic (EEG) epileptiform activity during sleep. We used the Epworth Sleepiness Scale questionnaire[24] together with medical history and physical examination to exclude sleep disturbance as a consequence of a medical or neurological disorder other than PD/Lewy body dementia (LBD)/multiple system atrophy (MSA), mental disorder, medication, or substance abuse.

The control group criteria included individuals who have no personal history or primary family history of PD or neurodegenerative disease. All individuals met the above inclusion criteria and matched members of the PD or RBD groups in age (± 3 y). All individuals underwent a Montreal Cognitive Assessment test (MoCA), and Unified Parkinson's Disease Rating Scale (UPDRS) evaluation with I-IV subscales. All individuals underwent clinical, behavioral, and fMRI testing in the off medicine state, defined as no PD medicines after 8:00 p.m. the night before. Table 1 illustrates demographic and clinical characteristics between groups.

Image Acquisition

Each participant participated in a single imaging session (Philips Intera 3T scanner, Philips Medical Systems, Bothell, WA). Patients with PD were off medication, as dopaminergic

therapy influences the fMRI signal during tasks[25] and at rest.[26] A T1-weighted magnetization-prepared rapid acquisition turbo field echo sequence was collected (repetition time/echo time [TR/TE] = 8.4/3.9 ms; flip angle = 8 degrees; matrix size = 256 × 256; field of view = 240 mm; slice thickness = 1.0 mm, sagittal acquisition), as well as a T2-weighted turbo spin-echo volume acquisition (TR/TE = 2500/367 ms; echo train length 120, pixel bandwidth 380, flip angle = 90 degrees, matrix size = 256 × 256; field of view = 240 mm, slice thickness = 0.94 mm, 186 sagittal slices). Finally, a whole-brain echo-planar imaging (EPI) run sensitive to BOLD contrast (TE = 30 ms; flip angle = 90 degrees; 2 sec TR; 150 dynamics; 2.75 × 2.75 × 3.5 mm voxel resolution) was acquired while participants were resting and instructed to remain still and fixate on a white crosshair displayed on a black background during the functional acquisition.

Image Processing

Image processing was performed in Analysis of Functional Neuroimages (AFNI).[27] Functional images were realigned to the native space skull-stripped T1-weighted MRI. The T2-weighted volume was also aligned to the T1-weighted MRI. Each participant's skull-stripped T1-weighted MRI was affine normalized to the Collins N27 template in Montreal Neurological Institute (MNI) space. This transformation was used to spatially normalize each aligned functional volume to MNI space, and also to place the high resolution T2 volume into MNI space. Each participant's 150 aligned and normalized fMRI images were processed according to standard resting state analysis methods with recommended processing steps and default parameters (http://afni.nimh.nih.gov/pub/dist/edu/latest/afni_handouts/instastuff.pdf) to prepare for group analysis, including voxelwise detrending by removal of a constant plus linear plus quadratic trend, bandpass filtering (passband 0.01-0.1 Hz), removal by regression of signal that covaried with the rotational and translational movement parameters from the EPI-to-T1 alignment, and smoothing in the spatial but not temporal domain of all within-brain voxels using a 6 mm full-width half-maximum filter.

Analysis of Head Movements during fMRI

The extent of motion during each participant's functional imaging run did not differ between groups. No significant differences (two-tailed t-tests, $P < 0.01$) in the range of the x, y, and z translational shift parameters (mm) were found among controls (x = 0.26, y = 0.81, z = 0.82), RBD (x = 0.38, y = 0.74, z = 0.74), and PD (x = 0.36, y = 1.33, z = 0.99) groups; no differences were found either in the range of each of the x, y, and z angular rotations (degrees) among controls (x = 0.28, y = 0.83, z = 0.27), RBD (x = 0.41, y = 0.65, z = 0.37), and PD (x = 0.30, y = 1.25, z = 0.40) groups.

Correlation Map Generation

Two seeds were used for the generation of correlation maps to be used as inputs to the voxelwise ANOVA. The first was in the left SN (LSN) [MNI coordinate: x = +11, y = +18, z = -9; Talairach coordinate = +11, +18, -7] and the second was in the right SN (RSN) [MNI coordinate = -11, +18, -9; Talairach coordinate: -11, +18,-7]. Seed locations were confirmed to be in SN using the acquired T2 MRI volumes, where the SN is most easy to see. A total of 62 correlation maps were constructed, 31 (1 per participant) consisting of voxelwise correlation coefficients with LSN and 31 correlation maps with RSN.

Voxelwise ANOVA

Differences in SN correlations among the three groups (controls, PD, RBD) were assessed with AFNI's *3dANOVA* function. First, each correlation map was Fisher-transformed [*arctanh(r)*]. Then, two voxelwise F-maps were computed. First, the L*S*N Fisher-transformed correlation coefficient maps were used to compute an F-map for the main effect of group. Then, the RSN Fisher-transformed correlation coefficient maps were used to compute an F-map for the main effect of group. Each of these F-maps was then thresholded at a corrected P value of $P < 0.01$ (uncorrected $P < 0.001$, $F = 8.76$) and a minimum cluster size of 64 voxels (512 mm^3), which was determined using AFNI's *3dClustSim* (2mm^3 grid, 152,834 voxels in mask, 10,000 iterations). This multiple comparison correction takes into account the number of whole-brain voxels and the smoothness of the residual noise distribution to obtain a P value that indicates the probability that a cluster of a certain size will occur by chance. AFNI's *3dclust* command was then used to find the MNI coordinate center of mass of each cluster surviving the P value and cluster extent threshold and to create a binary mask of those voxels comprising each cluster. Binary masks for each cluster were then used to extract the average correlation values from each participant's correlation coefficient maps. Finally, *post hoc t* tests were computed to determine the pattern of resting state change across groups in each cluster with the SN.

RESULTS

Differences in Demographic and Clinical Characteristics

There was no significant age difference between the PD, RBD, and age-matched control group of patients (Table 1). Cognitive function as measured by performance on the MoCA screening test was also not significantly different between the groups. Significant differences between PD versus controls and PD versus RBD for the Hoehn and Yahr staging and UPDRS-total score between PD versus controls emphasize the distinction of symptomatic motor impairment manifested in the PD patient group.

Voxelwise ANOVA of LSN Correlation Maps

The voxelwise ANOVA of LSN correlation maps produced an F-map with a single cluster that survived the whole-brain multiple comparison P value and cluster extent thresholds. This cluster of 96 voxels was located in the left putamen (MNI coordinate -23, +10, +2), and is displayed on an average of all participants spatially normalized T1 MRIs in Figure 1.

Post hoc t tests were conducted on the participant's average correlations within the left putamen cluster and revealed a pattern of highest correlation with LSN in the control group, lower correlations in the RBD group, and the lowest correlations in the PD group (Figure 2). The cluster correlations for patients with RBD are significantly lower compared to controls ($P = 0.0007$, $t_{(9)} = 5.00$) and significantly higher compared to patients with PD ($P = 0.002$, $t_{(10)} = 4.13$).

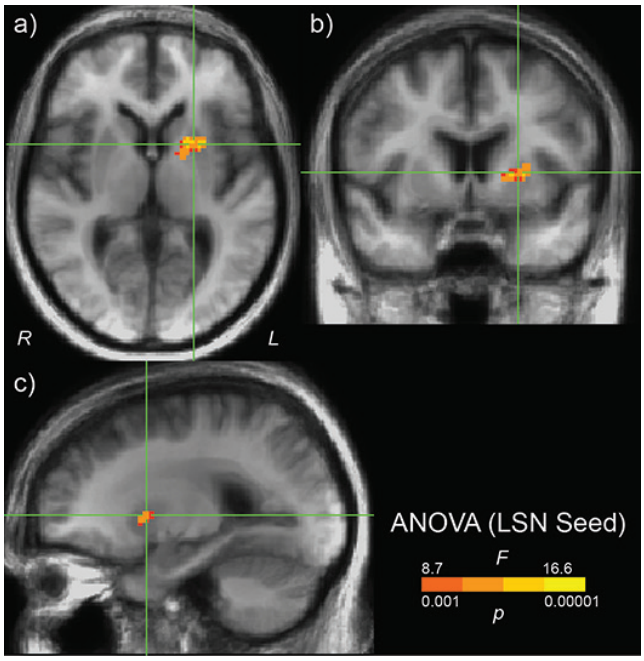

Figure 1—F-map from analysis of variance (ANOVA) of individual left substantia nigra (LSN) resting state correlation maps reveals a single cluster in left putamen. The left putamen cluster is displayed at a corrected (whole-brain) threshold of P < 0.01 (uncorrected P < 0.001, F = 8.76) in axial **(A)**, coronal **(B)**, and sagittal **(C)** views. The cluster size is 96 contiguous voxels (768 mm^3) and is located at Montreal Neurological Institute coordinate -23, +10, +2 (center of mass).

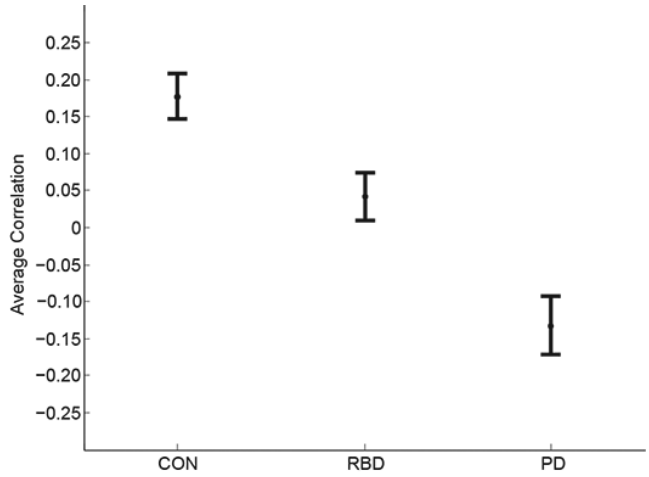

Figure 2—Patients with rapid eye movement sleep behavior disorder (RBD) show altered resting state correlations between left substantia nigra and left putamen compared to controls (CON) and patients with PD. Average correlations among participants are shown for the cluster of left putamen voxels depicted in the analysis of variance F-map of Figure 1. Left putamen cluster correlations for patients with RBD are significantly lower compared to controls (P = 0.0007, $t_{(9)}$ = 5.00) and significantly higher compared to patients with PD (P = 0.002, $t_{(10)}$ = 4.13).

Voxelwise ANOVA of RSN Correlation Maps

The voxelwise ANOVA of RSN correlation maps produced an F-map with two clusters that survived the whole-brain multiple comparison P value and cluster extent thresholds. The first cluster of 120 voxels was located in the right cuneus/precuneus (MNI coordinate +11, -72, +38), and is displayed on an average of all participants spatially normalized T1 MRIs in Figure 3. The cluster straddles the parieto-occipital sulcus (seen in Figure 3C) and encompasses portions of the cuneus[28] and precuneus.[29,30]

Post hoc t tests conducted on the participants' average correlations within the cluster of right cuneus/precuneus voxels (Figure 4) revealed a pattern of correlations in patients with RBD that were significantly higher compared to both controls (P = 0.0005, $t_{(9)}$ = 5.30) and patients with PD (P = 0.0001, $t_{(10)}$ = 5.81).

The second cluster of 68 voxels was located in the right superior occipital gyrus (MNI coordinate +20, -94, +16), and is displayed on an average of all participants spatially normalized T1 MRIs in Figure 5.

Post hoc t tests conducted on the participants' average correlations within the cluster of right superior occipital gyrus voxels (Figure 4) revealed a pattern of correlations (Figure 6) in which the control group showed the lowest correlations, the PD group showed the highest correlations, and the RBD group showed correlations in the middle of these two groups. The cluster correlations for patients with RBD are significantly higher compared to controls (P = 0.034, $t_{(9)}$ = 2.49) and significantly lower relative to patients with PD (P = 0.023, $t_{(10)}$ = 2.67).

DISCUSSION

In the current study, we found evidence for our primary hypothesis of altered functional connectivity between SN and striatum in patients with idiopathic REM sleep behavior disorder. In the voxelwise ANOVA of SN correlation maps, a cluster of significantly different connectivity was found in the left putamen among the three groups. Subsequent *t* tests revealed that patients with RBD showed reduced correlation magnitude relative to controls. Patients with PD showed even lower correlations in the left putamen, with correlation magnitudes significantly lower than the RBD group. This raises an important question: why is the magnitude of SN correlations significantly reduced in the left hemisphere of the RBD group but not in the right hemisphere?

The majority of the patients with PD studied (eight of 11) presented with more impaired movements on the right side, implying greater left hemisphere nigrostriatal dysfunction.[31] The greater reduction found in left versus right hemisphere SN-putamen functional connectivity is consistent with the movement onset asymmetry data. The reduced functional correlations in the PD group suggest resting-state fMRI may provide information about the breakdown of functional connectivity in a circuit known to degenerate during disease,[32] and that it may be a promising non-invasive complement to existing methods currently available to assess SN dysfunction in PD.[33]

The patients with RBD do not have detectible movement impairment on either side, yet their SN correlations are asymmetrically reduced on the left side. One explanation for this is that there exists left hemispheric predominance of nigrostriatal dysfunction during the development of PD, and that these asymmetrical biological changes occur early in the disease progression before the onset of noticeable behavioral impairment. A recent study found evidence of asymmetry of dopaminergic denervation that was left sided in right-handed patients

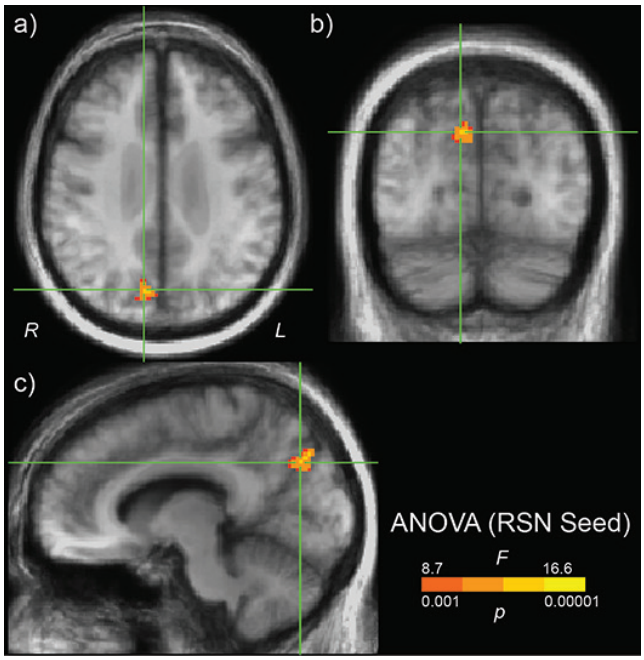

Figure 3—F-map from analysis of variance (ANOVA) of individual right substantia nigra resting state correlation maps reveals the largest cluster in right cuneus/precuneus. The right cuneus/precuneus cluster is displayed at a corrected (whole-brain) threshold of P < 0.01 (uncorrected P < 0.001, F = 8.76) in axial **(A)**, coronal **(B)**, and sagittal **(C)** views. The cluster size is 120 contiguous voxels (960 mm^3) and is located at Montreal Neurological Institute coordinate +11, -72, +38 (center of mass).

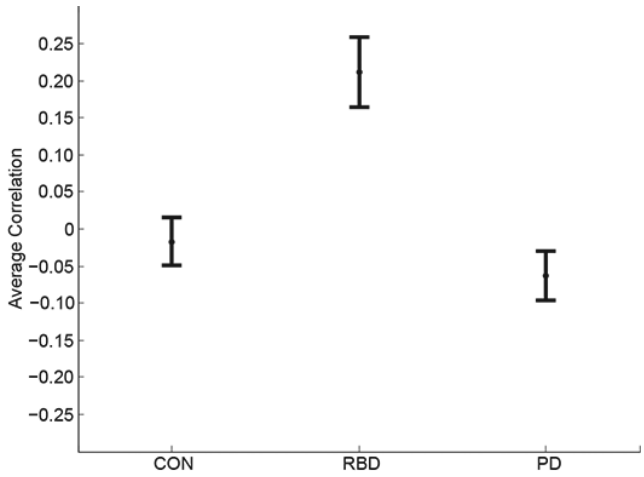

Figure 4—Patients with rapid eye movement sleep behavior disorder (RBD) show elevated resting state correlations between right substantia nigra and right cuneus/precuneus compared with controls (CON) and patients with PD. Average correlations are shown for the cluster of right cuneus/precuneus voxels depicted in the analysis of variance F-map of Figure 3. Correlations in the right cuneus/precuneus cluster are significantly higher for patients with RBD compared with both controls (P = 0.0005, $t_{(9)}$ = 5.30) and patients with PD (P = 0.0001, $t_{(10)}$ = 5.81).

with right-sided symptoms.[18] If a significant fraction of the patients with RBD studied here eventually develop PD, it may be that degeneration is occurring asymmetrically in these patients presymptomatically, and a correlate of this dysfunction is reduced LSN-left putamen resting state connectivity. The interpretation that the functional correlation reductions in the nigrostriatal system of the RBD group may diminish asymmetrically well before obvious motor symptoms appear cannot be made until all patients with RBD are followed over the long term to see how many convert to a diagnosis of PD, or in whom other degenerative disorders such as MSA or LBD are diagnosed.[34] The predictive value of the SN-putamen functional correlation metric for various disorders will be evaluated at the end of a larger ongoing longitudinal study of these patients. It is worth noting that of the 10 patients with idiopathic RBD reported here, one converted to PD 1 y after initial imaging, and this patient was one of the 60% with reduced SN-putamen magnitudes. It is also important to emphasize that resting state correlations of BOLD-fMRI, an indirect measure of neuronal activity related to postsynaptic local field potentials,[35] cannot be used to infer anything about dopamine function *per se*. Reduced dopaminergic striatal innervation can be assessed with nuclear imaging to distinguish PD from essential tremor.[36] A reasonable hypothesis is that as dopaminergic innervation of striatum decreases, the BOLD-fMRI correlation magnitude between regions also may decrease. The results presented here are consistent with this hypothesis, but require validation using BOLD-fMRI and nuclear imaging techniques in the same patients.

In addition to testing the primary hypothesis that patients with RBD show reduced nigrostriatal connectivity, a whole-brain voxelwise ANOVA was conducted to search for other areas, including those in cortex, that distinguished the RBD group from controls and patients with PD. Two right hemisphere cortical areas correlated with RSN differed among groups and survived the whole-brain multiple comparisons correction. The first was located in the right cuneus/precuneus, and near Brodmann area 7. Patients with RBD showed elevated connectivity compared with both controls and patients with PD, suggesting that in the right hemisphere the SN and cuneus/precuneus is functionally hyperconnected. The cuneus, precuneus, and other regions of the posteromedial regions of the parietal lobe are implicated in a variety of highly integrated tasks, including visuospatial imagery, memory retrieval, attention, self-processing operations, and sleep,[37] and are known to be connected to the striatum. The posteromedial cortex is selectively hypometabolic in sleep, vegetative states, and during anesthesia. It is also selectively deactivated relative to other brain areas during REM sleep,[38,39] although the precise reason for this is not entirely clear. Increased posteromedial connectivity could be related to the reduced complex cognitive abilities, including attention, memory, and visuospatial abilities, reported to accompany RBD.[40-42] Other imaging data reveal specific changes near the cuneus/precuneus of patients with RBD,[43] indicating some alteration of metabolism accompanies idiopathic RBD. Similar perfusion changes also have been reported in the less affected hemisphere of patients with *de novo* PD,[44] which in our group would correspond to the right hemisphere, where significant connectivity increase in SN-cuneus/precuneus is found.

Although increased SN-cuneus/precuneus functional connectivity in the RBD group was found, there was no significant increase in SN-cuneus/precuneus connectivity in the PD

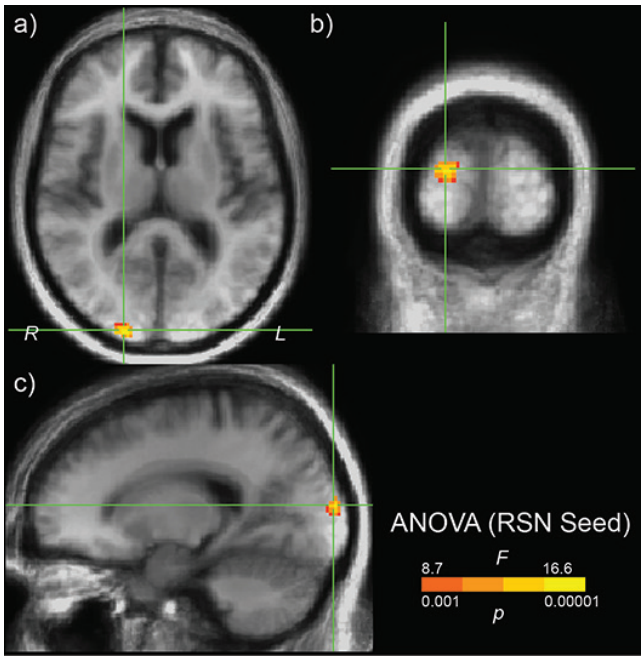

Figure 5—F-map from analysis of variance (ANOVA) of individual right substantia nigra (RSN) resting state correlation maps reveals a smaller cluster in the right superior occipital gyrus. The superior occipital gyrus cluster is displayed at a corrected (whole-brain) threshold of P < 0.01 (uncorrected P < 0.001, F = 8.76) in axial **(A)**, coronal **(B)**, and sagittal **(C)** views. The cluster size is 68 contiguous voxels (544 mm^3) and is located at Montreal Neurological Institute coordinate +20, -94, +16 (center of mass).

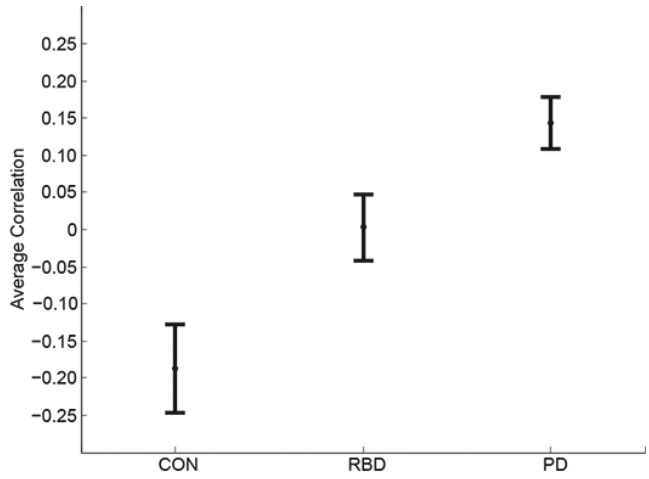

Figure 6—Patients with rapid eye movement sleep behavior disorder (RBD) show altered resting state correlations between right substantia nigra and right superior occipital gyrus compared with controls (CON) and patients with PD. Average correlations among participants are shown for the cluster of right superior occipital gyrus voxels depicted in the analysis of variance F-map of Figure 5. Right superior occipital gyrus cluster correlations for patients with RBD are significantly higher compared to controls (P = 0.034, $t_{(9)}$ = 2.49) and significantly lower relative to patients with PD (P = 0.023, $t_{(10)}$ = 2.67).

group relative to controls. The lack of increased SN-cuneus/precuneus PD connectivity is notable because all except one of the patients with PD has RBD. There are at least two possibilities to explain this finding. The first is that a number of the patients with RBD studied here will not go on to develop PD, and the increased SN-cuneus/precuneus functional connectivity reflects some unique pathophysiology of the RBD group that is not shared by the PD group. The second possibility is that the functional connectivity profile that evolves over months to years from RBD to PD with RBD is nonlinear. For example, in PD, it is known that there is a complex relationship between specific cognitive problems faced by patients and the specific stage of their disease,[45] and that separate corticosubcortical circuits are differentially affected by the cortical and subcortical pathophysiological changes during the course of the disease.[46] Therefore, it would not be surprising if the progression from RBD to PD with RBD involves increases and decreases in different subcortical-cortical connections at different times. We cannot rule out either one of these two scenarios in the current study. Additional longitudinal imaging would be helpful in clarifying patterns of changes that occur at different points in time. Because increased cuneus/precuneus connectivity was not predicted at the outset of the current study, further investigation is required in larger samples of patients with RBD.

The second cortical area showing differences among groups was the right superior occipital gyrus, which demonstrated the lowest magnitude correlation with RSN in the control group, significantly higher correlation magnitude in the patients with RBD, and the highest correlation in patients with PD. Coactivation and connectivity of SN with occipital visual areas has been reported previously[47,48] so there is some anatomical basis for the changes found in the current study. Additionally, EEG studies of patients with RBD demonstrate increased delta and theta activity compared to controls in right hemisphere occipital regions during wakefulness,[49] which fits with the increased right hemisphere connectivity found in the RBD group relative to controls during our resting state scan. Visual and perceptual deficits are reported as one nonmotor complication in PD, with visual and eye movement studies showing a link to the visual system and specifically altered occipital metabolism in PD.[50] Higher stimulus-related EEG gamma activity has been reported under some circumstances in PD versus controls,[51] suggesting the possibility of dopaminergic alteration of visual-evoked gamma activity. As with the changes in SN-cuneus/precuneus activity, the right occipital connectivity differences were not specifically predicted at the outset of this study so they must be replicated and explored further in another sample of patients with RBD and PD.

In conclusion, the results of this fMRI-BOLD resting state study demonstrated altered nigrostriatal and nigrocortical correlations in RBD relative to controls and patients in whom PD was diagnosed. The application of resting state methods to characterize the patients with RBD is in the early stages, but holds promise for developing biomarkers for diagnosis and disease progression, especially as patients with RBD develop PD and other synucleinopathies.[52] The reduced nigrostriatal correlations in RBD are consistent with hypotheses of dopaminergic degeneration, although contributions of other pathogenic processes in RBD cannot be ruled out.[53] Differences found in right hemisphere SN connectivity fit generally with the complex network of cortical changes accompanying cognitive impairment in PD,[54] but much work remains to fully characterize

these changes in RBD and develop them as early markers of neurodegeneration.

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