

## Mesocorticolimbic Hemodynamic Response in Parkinson's Disease Patients With Compulsive Behaviors

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**ABSTRACT: Background:** PD patients treated with dopamine therapy can develop maladaptive impulsive and compulsive behaviors, manifesting as repetitive participation in reward-driven activities. This behavioral phenotype implicates aberrant mesocorticolimbic network function, a concept supported by past literature. However, no study has investigated the acute hemodynamic response to dopamine agonists in this subpopulation.

**Objectives:** We tested the hypothesis that dopamine agonists differentially alter mesocortical and mesolimbic network activity in patients with impulsive-compulsive behaviors.

**Methods:** Dopamine agonist effects on neuronal metabolism were quantified using arterial-spin-labeling MRI measures of cerebral blood flow in the *on*-dopamine agonist and *off*-dopamine states. The within-subject design included 34 PD patients, 17 with active impulsive compulsive behavior symptoms, matched for age, sex, disease duration, and PD severity.

**Results:** Patients with impulsive-compulsive behaviors have a significant increase in ventral striatal cerebral blood flow in response to dopamine agonists. Across

all patients, ventral striatal cerebral blood flow *on*-dopamine agonist is significantly correlated with impulsive-compulsive behavior severity (Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease- Rating Scale). Voxel-wise analysis of dopamine agonist-induced cerebral blood flow revealed group differences in mesocortical (ventromedial prefrontal cortex; insular cortex), mesolimbic (ventral striatum), and midbrain (SN; periaqueductal gray) regions.

**Conclusions:** These results indicate that dopamine agonist therapy can augment mesocorticolimbic and striato-nigro-striatal network activity in patients susceptible to impulsive-compulsive behaviors. Our findings reinforce a wider literature linking studies of maladaptive behaviors to mesocorticolimbic networks and extend our understanding of biological mechanisms of impulsive compulsive behaviors in PD. © 2017 International Parkinson and Movement Disorder Society

**Key Words:** cerebral blood flow; dopamine; impulsive compulsive behaviors; impulse control disorder; Parkinson's disease

Impulsive-compulsive behaviors (ICBs) are a well-described side effect of dopamine agonist (DAgonist) therapy in patients with Parkinson's disease (PD), with an estimated prevalence of 15% to 40% in treated patients.<sup>1,2</sup> Patients with ICBs (ICB<sup>+</sup>) present with

compulsive participation in reward-driven activities, which include sex, eating, gambling, shopping, or hobby participation.<sup>2,3</sup> While not all patients with PD appear susceptible to ICBs, reduction or discontinuation of DAgonist medications in ICB<sup>+</sup> patients often

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results in behavioral improvement.<sup>4</sup> Given that commonly prescribed medications (e.g., pramipexole and ropinirole) preferentially target D2-like receptors (D3 > D2), it is hypothesized that patients susceptible to ICBs may have heightened mesocorticolimbic response to DAgonist therapy.<sup>5,6</sup> This hypothesis is based on behavioral studies that show increased risk preference in response to DAgonists in ICB<sup>+</sup> patients and evidence of altered D2-like receptor density in this network.<sup>7-9</sup>

Indeed, neuroimaging studies demonstrate that ICB<sup>+</sup> patients have a functionally unique mesocortical and mesolimbic (e.g., ventral striatum) response to risk- and reward-based cues, and altered cerebral blood flow (CBF) to this region.<sup>10</sup> PET and single-positron emission computed tomography studies show that dopamine-related neurotransmission differs in ICB<sup>+</sup> patients, where studies report lower striatal dopamine transporter levels, lower ventral striatal D3-receptor binding, and higher dopamine receptor binding in the orbitofrontal cortex.<sup>8,11,12</sup> There is no imaging evidence that acute administration of DAgonists results in distinct mesocorticolimbic changes in ICB<sup>+</sup> patients, despite empirical evidence suggesting that behavioral symptoms are linked to medication-induced alterations to reward circuits.

One barrier to interrogating these relationships is that it is difficult to perform quantitative surveillance imaging of regional brain activity with methods that require exogenous contrast agents or ionizing radiation attributed to dose restrictions. Arterial spin labeling (ASL)-MRI provides a quantitative hemodynamic measure of CBF (mL blood/100g tissue/min) by using endogenous arterial blood water magnetization as a noninvasive tracer.<sup>13,14</sup> CBF is closely related to neuronal activity and glucose metabolism.<sup>15</sup> ASL produces a more direct quantitative marker of brain function compared to more commonly utilized blood oxygenation level-dependent MRI, which provides a qualitative susceptibility-weighted contrast secondary to changes in blood oxygenation level in and around draining veins and, as such, is difficult to compare quantitatively between repeated scans.<sup>16</sup> Only one ASL study has investigated ICB in the context of PD patients in the *on*-dopamine medicated state, with findings suggesting decreased ventral striatal CBF in ICB<sup>+</sup> patients.<sup>10</sup>

The purpose of this study was to improve our understanding of the brain circuits mediating DAgonist-induced behaviors by evaluating CBF in PD patients with and without active ICB symptoms in the *off*-medication and *on*-DAgonist states. Because the majority of ICBs emerge following DAgonist exposure, we hypothesized that ICB<sup>+</sup> patients would have different CBF responses to DAgonist in mesocorticolimbic regions than PD patients without ICB (ICB<sup>-</sup>).

Secondary goals were to investigate whether (1) regional CBF changes vary between ICB patient groups in the *off*-medication state and (2) the CBF DAgonist response portends ICB severity.

## Patients and Methods

### Participants

Subjects (n = 34; sex = 12 F/22 M; age = 61.7 ± 8.8 years) were recruited from the Movement Disorders Clinic at Vanderbilt University and provided written, informed consent in accord with the institutional review board. Inclusion criteria were: (1) idiopathic PD meeting UK Brain Bank criteria and (2) present use of DAgonist therapy. Exclusion criteria were: (1) implanted deep brain stimulator; (2) concurrent use of other psychoactive medications that could alter neuronal metabolism and CBF; and (3) presence of other major neuropsychiatric, cerebrovascular, or cardiovascular disease (see the Supporting Information for full criteria). Medication regimens were recorded, and all DAgonist dosages were converted to levodopa equivalent dose (LEDD).<sup>17</sup> A cognitive screen was performed using the Montreal Cognitive Assessment (MoCA), and premorbid intelligence screened using the American version of the National Adult Reading Test (AMNART).<sup>18,19</sup> Depression symptoms were screened using the Center for Epidemiologic Studies Depression Scale Revised (CESD-R).<sup>20</sup> The extent of cognitive symptoms was assessed by a board-certified neurologist (DOC), to ensure that all subjects possessed adequate insight to consent to the study and accurately respond to behavioral questionnaires. Clinically significant anxiety disorders that would prevent participation in the imaging and medication withdrawal study (e.g., claustrophobia) were also screened through this interview.

### Nonimaging Procedures

Active ICB symptom evaluation was based on a detailed semistructured behavioral interview with the patient and spouse. This interview evaluated the presence of compulsive behaviors with initial onset or increased intensity following DAgonist administration, with specific attention toward previously reported categories of compulsive shopping, eating, hypersexuality, gambling, and hobbyism.<sup>3,21,22</sup> If meeting the criteria for (1) present symptoms and (2) emergence of symptoms after the initiation of DAgonist, patients were designated as ICB<sup>+</sup>. Participants also completed three self-report scales: the Barrett Impulsivity Scale (BIS); the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS); and International Parkinson and Movement Disorder Society-UPDRS (MDS-UPDRS) part II (an assessment of the impact of PD on activities of daily living).<sup>22-24</sup>

From the 90 PD patients who had completed the initial screening and behavioral interview, 17 were determined to be ICB<sup>+</sup> and were enrolled in the imaging portion of the study. 17 ICB<sup>-</sup> patients matched for age and UPDRS-II severity were also enrolled to ensure size-matched groups.

Before MRI scanning, patients underwent clinical examination by a board-certified neurologist to assess PD symptom severity using MDS-UPDRS III<sup>24</sup> in the *on*-DAgonist and *off*-Dopamine (L-dopa+DAgonist) state. In the *off* condition, patients refrained from all dopaminergic medications (at least 36 hours for DAgonist and 16 hours for L-dopa) before assessments, because this period is sufficient to eliminate DAgonist effects (the half-life of immediate-release DAgonists, e.g., ropinirole and pramipexole, is approximately 6 hours<sup>25</sup>). In the *on*-DAgonist state, patients were evaluated after taking their prescribed DAgonist medication, having withheld L-dopa for at least 16 hours. Extended release DAgonist compounds (taken by 5 ICB<sup>+</sup> and 6 ICB<sup>-</sup> patients) were administered 6 hours before scanning, whereas non-extended release DAgonists (taken by 12 ICB<sup>+</sup> and 11 ICB<sup>-</sup> patients) were administered 2 hours before scanning.

### MRI

MRI scanning was performed at 3.0 Tesla (Philips Healthcare, Best, The Netherlands) in the *off*- and *on*-DAgonist states. All subjects underwent a multimodal imaging protocol consisting of: (1) T<sub>1</sub>-weighted (three-dimensional magnetization-prepared rapid gradient echo; spatial resolution = 1 × 1 × 1 mm<sup>3</sup>; repetition time [TR]/echo time [TE] = 8.9/4.6 ms); (2) T<sub>2</sub>-weighted fluid attenuated inversion recovery (spatial resolution = 1 × 1 × 1 mm<sup>3</sup>; TR/TE = 4,000/120 ms); and (3) CBF-weighted pseudo-continuous ASL (two-dimensional single-shot echo-planar-imaging; slices = 20; spatial resolution = 3.5 × 3.5 × 5 mm<sup>3</sup>; TR/TE = 4,000/11 ms with postlabeling delay (PLD) and labeling pulse train = 1,500 ms). The scan time for the pseudo-continuous arterial spin labeling (pCASL) sequence was 4 minutes 48 seconds, whereas the scan time for the full imaging protocol was approximately 35 minutes.

### Image Analysis

CBF quantification was performed in Matlab (The Mathworks, Inc., Natick, MA). Data were motion-corrected and surround-subtracted, and the mean across all averaged measurements was computed to obtain a mean difference magnetization ( $\Delta M$ ). The difference magnetization was then normalized by the equilibrium magnetization ( $M_0$ ), slice-time corrected (readout duration per slice = 23 ms), and converted to absolute CBF (mL/100 g/min).<sup>26</sup> It was also possible that motion differed between scans acquired in the

*off*- versus *on*-DAgonist states. To evaluate this possibility, we also recorded the variance of the motion-corrected images over time for each subject.

Next, T<sub>1</sub>-weighted images were skull-stripped and total gray matter, along with major subcortical regions, including hippocampus, amygdala, pallidum, ventral striatum, putamen, and caudate, were segmented using FSL-FIRST.<sup>27</sup> These subcortical regions of interest (ROIs) were chosen because they are implicated in the functioning of reward-related networks and contain elevated densities of D2-like receptors.<sup>6,28</sup> The ASL images were coregistered to the native T<sub>1</sub>-weighted subject image in preparation for voxel-wise mapping to an isotropic 2-mm T<sub>1</sub>-weighted atlas (Montreal Neurological Institute).<sup>29</sup> CBF maps in native T<sub>1</sub>-weighted space were used to determine the CBF in the above subcortical regions. Note that when subject-specific regions are used, the analysis accounts for possible differences in structure size that could otherwise bias CBF values if standard ROIs are used. The following variables were preserved for hypothesis testing: (1) volumes (mm<sup>3</sup>) of the major subcortical regions outlined above; (2) CBF (mL/100 g/min) values in total gray matter and subcortical regions, separately recorded in *off*-DAgonist and *on*-DAgonist states; (3) fractional CBF changes ( $[\text{CBF}_{\text{On-DAgonist}} - \text{CBF}_{\text{Off-DAgonist}}] / \text{CBF}_{\text{Off-DAgonist}}$ ); and (4) CBF maps in standard space.

### Statistical Analysis

Data distributions were inspected through the use of QQ plots, and CBF values more than 2.5 standard deviations (SDs) beyond the group mean were considered outliers and removed.

Demographic and clinical parameters were evaluated using a Mann-Whitney U test, excepting sex (evaluated using a chi-square test). To test the primary hypothesis that ICB<sup>+</sup> patients have significantly different CBF responses to DAgonist therapy than ICB<sup>-</sup> patients, CBF responses to DAgonist in the segmented subcortical regions were compared using a Mann-Whitney U test. For each group, we considered mean hippocampus, amygdala, pallidum, putamen, caudate, and ventral striatum, leading to six comparisons. Significance was defined as Bonferroni-corrected two-sided  $P < 0.05$ . To ensure that group differences in CBF response were not a result of potential confounding factors, any subcortical regions observed as significantly different between groups were considered in a post-hoc one-way analysis of covariance (ANCOVA) model, including age, sex, volume of the given ROI, UPDRS part III (*off*-DAgonist), DAgonist single-dose equivalent, L-dopa daily dose, and MoCA score as covariates. The significance criterion was two-sided  $P < 0.05$ .

As a supplemental analysis, we also investigated whether the *off*-DAgonist regional CBF differed

**TABLE 1.** Demographic and clinical evaluation from the two participant groups

Variables	PD ICB <sup>-</sup>	PD ICB <sup>+</sup>	P Value
N	17	17	
Sex (M/F)	12/5	10/7	0.47
Age (years)	62.5 ± 10.4	61.0 ± 7.1	0.32
Disease duration (years)	5.8 ± 4.5	6.4 ± 3.8	0.54
MoCA	24.7 ± 2.7	26.4 ± 2.1	0.05
AMNART	118.2 ± 8.3	117.2 ± 8.7	0.77
CES-D	14.4 ± 6.8	17.7 ± 11.4	0.51
MDS-UPDRS			
Part II	22.8 ± 7.8	21.9 ± 9.9	0.42
Part III (OFF)	32.9 ± 12.2	25.8 ± 11.1	0.07
Part III (ON)	23.7 ± 10.9	15.5 ± 7.1	0.01 <sup>a</sup>
QUIP-RS total	19.0 ± 11.4	36.6 ± 9.6	<0.0001 <sup>a</sup>
BIS total	59.1 ± 9.0	66.9 ± 11.8	<0.05 <sup>a</sup>
ICB symptom distribution (based on semistructured behavioral interview)			
Hobbyism	n/a	11/17	
Eating	n/a	12/17	
Sex	n/a	10/17	
Shopping	n/a	4/17	
Gambling	n/a	0/17	
Laterality score (- = left worse; + = right worse)	-2.8 ± 9.8	-3.5 ± 11.3	0.86
Side of PD onset (L/R/bilateral)	9/7/0	8/7/2	
Dopamine replacement therapy			
Total LEDD (mg/day)	600.6 ± 400.3	666.1 ± 429.9	0.97
Agonist single-dose equivalent (mg/day)	99.4 ± 64.2	116.1 ± 76.0	0.51

Data are shown as mean ± SD.

MDS-UPDRS Part III (OFF) indicates that patients were *off*-DAgonist and *off*-L-dopa.

MDS-UPDRS Part III (ON) indicates that patients were *on*-DAgonist and *off*-L-dopa.

PD ICB<sup>-</sup> refers to PD without ICBs; PD ICB<sup>+</sup> refers to PD with symptoms consistent with ICB.

<sup>a</sup>Indicates uncorrected  $P < 0.05$ .

n/a, not applicable.

between groups by applying a Mann-Whitney U test with two-sided  $P < 0.05$  required for significance. This test was completed in order to determine whether results of the primary analysis were attributed to group CBF differences not related to acute DAgonist administration. To determine whether motion differed between *on*-DAgonist and *off*-DAgonist states, we applied a Wilcoxon signed-rank test to evaluate the temporal variance of motion-corrected data in each subject between the two time points. To understand whether CBF responses were related to a quantitative marker of impulsivity or were driven by motor disability, the CBF responses to DAgonist in the above regions and ventromedial prefrontal cortex were compared with QUIP-RS and (*off*-DAgonist) UPDRS-III motor scores using a Spearman's rank-order test (significance criteria: two-sided  $P < 0.05$ ).

Finally, an exploratory aim was to evaluate whether voxel-based image analysis delineated additional regional differences in CBF response to agonist using group status (e.g., ICB<sup>+</sup> or ICB<sup>-</sup>) as an exploratory variable. CBF maps in standard space were incorporated into a mixed-effects modeling of variance using the FSL FLAME algorithm<sup>30</sup> (significance,  $P < 0.01$ ). The analysis was performed over a standard atlas (2 mm) with a mask composed of total gray matter; cerebellum and occipital lobes were excluded because of

insufficient volume coverage in a subgroup of volunteers.

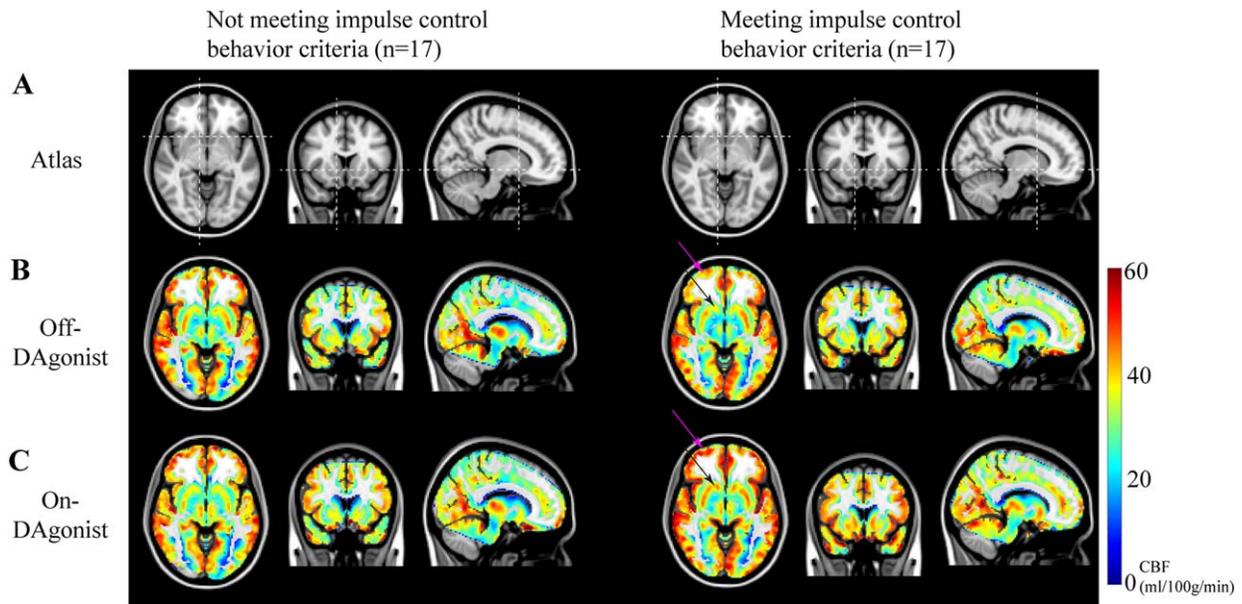
## Results

### Demographics

Demographic information for ICB<sup>+</sup> and ICB<sup>-</sup> patients is presented in Table 1. QUIP-RS scores were significantly greater in ICB<sup>+</sup> patients (uncorrected  $P < 0.0001$ ), with a trend for greater BIS score (uncorrected  $P = 0.045$ ). Groups were matched for UPDRS-II severity, and ICB<sup>+</sup> patients experienced greater UPDRS-III motor improvement in the *on*-DAgonist state (uncorrected  $P = 0.0139$ ). ICB<sup>-</sup> patients had a trend for a lower MoCA score (uncorrected  $P = 0.05$ ). Groups did not have significantly different side of motor onset or lateralized symptom severity. DAgonist and L-dopa daily doses in the *on* condition were not significantly different between groups.

### CBF and ICB Status

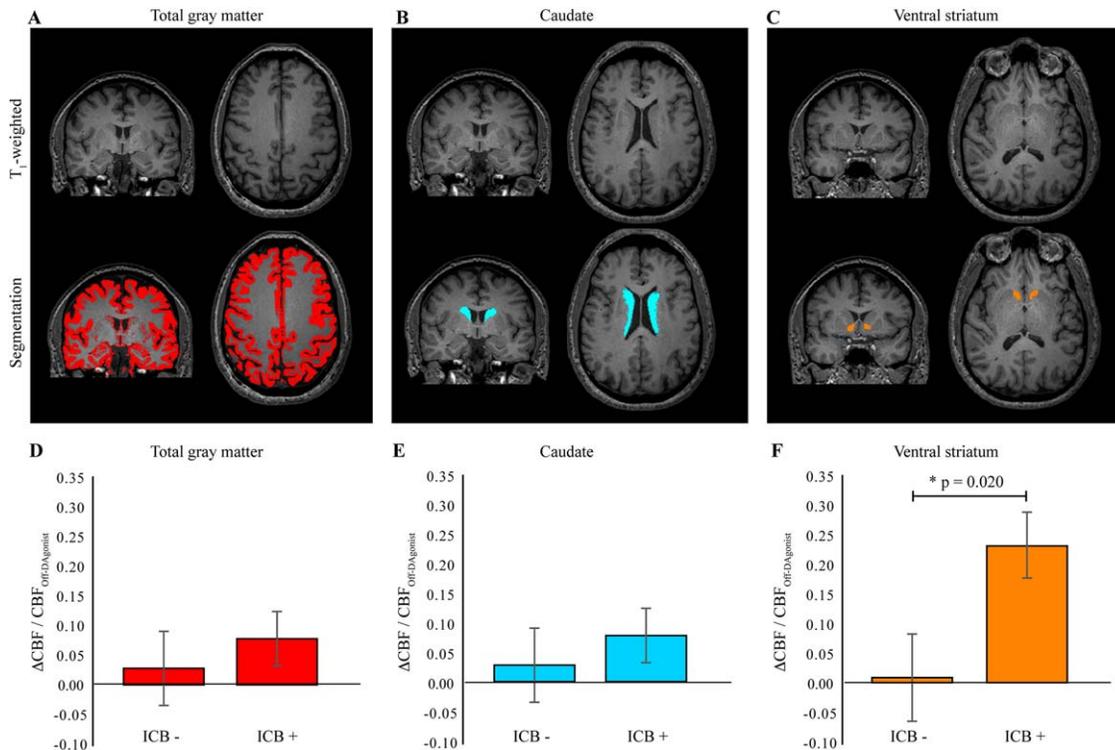
Figure 1 displays orthogonal representations of the mean CBF maps overlaid on the standard atlas for the ICB<sup>-</sup> and ICB<sup>+</sup> patients, separately for *off*-DAgonist and *on*-DAgonist states. Representative single-subject data are shown in Supporting Figure 1. Mean CBF in



**FIG. 1.** CBF response to DAgonist. (A) Orthogonal representation of the 2-mm T<sub>1</sub>-weighted structural atlas, along with (B) quantitative CBF values (mL/100 g/min) in the *off*-DAgonist and (C) *on*-DAgonist states for ICB<sup>-</sup> (left) and ICB<sup>+</sup> (right) patients. Limited CBF changes are observed in the ICB<sup>-</sup> group, yet increases in CBF in striatal (black arrow) and frontal (magenta arrow) regions are observed in the ICB<sup>+</sup> patients.

the *off*-DAgonist state was not significantly different between groups. However, increases in CBF were observed in the ICB<sup>+</sup> group in the *on*-DAgonist state,

which localized primarily to striatum and frontal cortex. By contrast, no significant increases were observed in the ICB<sup>-</sup> group (Fig. 1). When all data were



**FIG. 2.** Subcortical structural and CBF analysis. (A–C) Representative coronal and axial slices for a single subject show an example of the automated segmentation routine for three different structures, including (A) total gray matter, (B) caudate, and (C) ventral striatum. (D–F) Bar graphs of the mean CBF change in response to agonist in the three aforementioned regions for the ICB<sup>+</sup> and ICB<sup>-</sup> patients, with the error bars representing the SD of all subjects in each group, respectively. There was no significant difference in CBF change in (D) total gray matter or (E) caudate, but there was a significantly increased CBF change localized to the (F) ventral striatum in the ICB<sup>+</sup> group compared to the ICB<sup>-</sup> group. In order to emphasize the specificity of significant CBF change to the ventral striatum, gray matter and caudate are displayed to illustrate the lack of response in global (gray matter) and dorsal striatal (caudate) regions.

considered, a significant increase in CBF on DAgonist was evident in the ventral striatum ( $P = 0.030$ ). Bilateral ventral striatum showed a 23.1% increase in CBF in response to DAgonist in the ICB<sup>+</sup> group. The majority of subcortical regions showed small CBF increases of 5% to 8% in the ICB<sup>+</sup> group; however, these changes were not statistically significant (all  $P > 0.20$ ). When the ventral striatal CBF response was considered in the ANCOVA model, the group difference remained significant ( $P = 0.019$ ).

No significant differences were observed in residual motion of the dynamic images following motion correction ( $P = 0.53$ ). Total gray matter CBF response was not significantly different between groups ( $P = 0.410$ ; Fig. 2).

### CBF and Behavioral Metrics

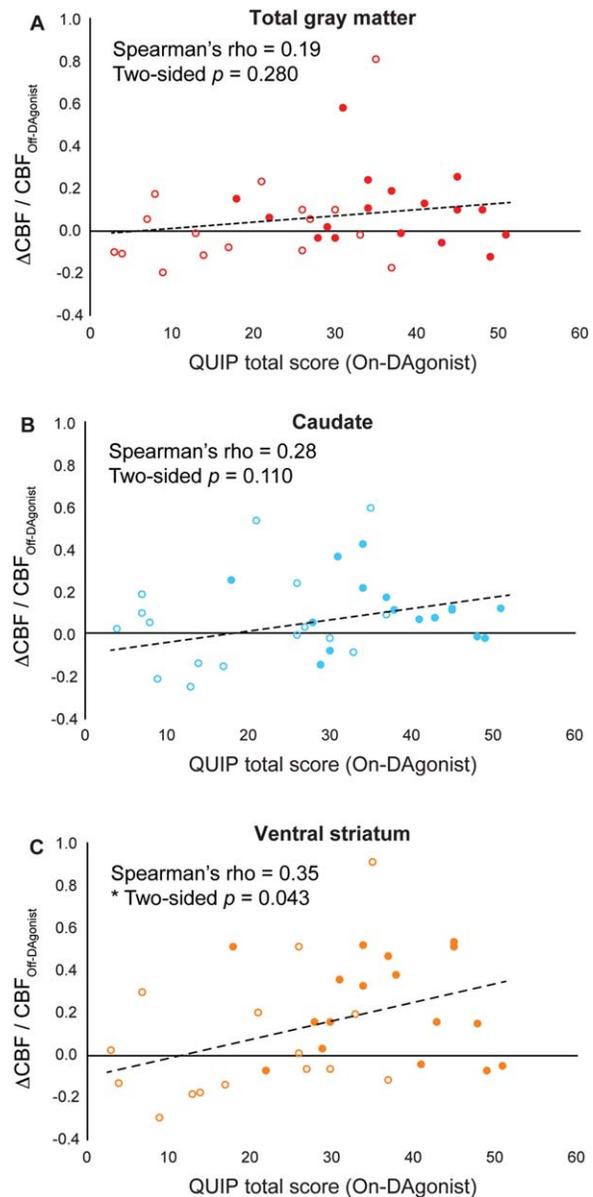
Figure 3 displays the relationship between CBF change in bilateral ventral striatum and DAgonist and QUIP-RS scores, showing a positive relationship. Individuals exhibiting higher levels of impulsivity on clinical evaluation had larger changes in CBF in the region ( $\rho = 0.35$ ;  $P = 0.043$ ). No trend between QUIP-RS and CBF change was observed in any of the other subcortical regions or global brain. No significant relationship between ventral striatal CBF response and motor improvement as quantified by UPDRS-III score was observed, suggesting that the ventral striatum CBF response is uniquely associated with impulsivity and not related to changes in motor symptomatology.

### Voxel-Based CBF Image Analysis

Figure 4 summarizes the results of the voxel-based analysis of CBF responses to DAgonist, separately for the two groups. The analysis was restricted broadly to the mesocortical and mesolimbic regions (Supporting Fig. 3) and served as a method of evaluating concerted network effects not captured by ROI analysis. Significant increases in CBF were observed in the bilateral striatum, SN, periaqueductal gray matter, insular cortex, and ventromedial prefrontal cortex relative to the ICB<sup>-</sup> group.

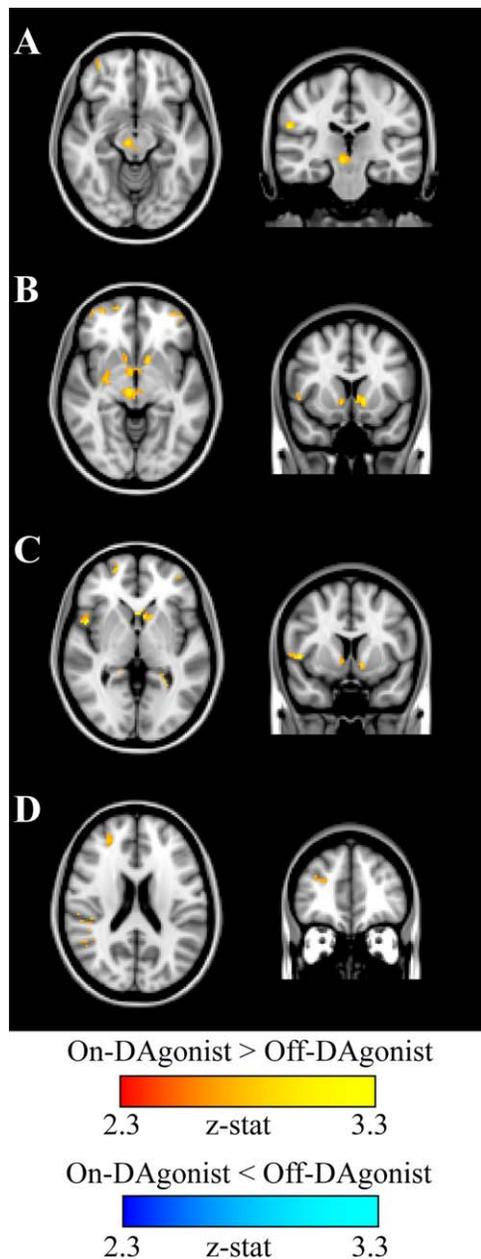
## Discussion

We show that ICB<sup>+</sup> PD patients have a distinct mesocorticolimbic and striatonigral cerebral blood flow response to DAgonist therapy. Consistent with our primary hypothesis, acute administration of commonly prescribed DAgonist medications induced changes to CBF in key regions of these networks, especially the ventral striatum. Furthermore, the ventral striatal CBF response correlated with scores in the QUIP-RS, a well-validated clinical screening tool. Voxel-wise analysis also revealed increased CBF in frontal, striatal, and midbrain regions. This effect is unlikely to be caused by differences in demographic variables,



**FIG. 3.** Relationship between CBF response to agonist and QUIP-RS score on-DAGonist in all patients. Open circles indicate ICB<sup>-</sup> individuals, and closed circles indicate ICB<sup>+</sup> individuals. The relationship is plotted for three structures, including (A) total gray matter, (B) caudate, and (C) ventral striatum. In a similar manner to Figure 2, gray matter and caudate were selected as representatives of global and dorsal striatal regions, respectively, to better visualize specific localization of a CBF/QUIP-RS relationship to the ventral striatum. These data demonstrate that in the ventral striatum, the CBF response is highest in subjects with greater QUIP-RS scores, indicative of increased levels of impulsivity. These data are consistent with CBF changes in response to DAgonist in ventral striatum correlating with behavioral phenotype. This relationship is not evident in total gray matter or caudate, implying that it is localized to the ventral striatum and not a global or generalized striatal effect. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

attributed to the use of within-subject off/on DAgonist comparisons in the study design, the fact that the two groups are well matched, and the preservation of the ventral striatal group CBF difference when possible confounds were included in an ANCOVA model. Given that CBF is a surrogate marker of neuronal



**FIG. 4.** Results of the voxel-wise analysis of CBF response to DAgonist. (A) Orthogonal slices from the 2-mm  $T_1$ -weighted atlas, along with regions that show positive and negative changes in CBF with DAgonist for ICB<sup>+</sup> patients relative to the ICB<sup>-</sup> patients. Positive changes after DAgonist administration are shown by the red-yellow scale, with yellow signifying a greater z-stat, and negative changes after DAgonist are shown by the dark blue-light blue scale, with light blue signifying the greater z-stat. All gray matter regions were included in analysis, with the exception of bi-occipital lobes and cerebellum where slice coverage was incomplete in some subjects. ICB<sup>-</sup> patients exhibit limited changes in CBF in response to agonist, whereas ICB patients showed more widespread patterns of changes throughout the striatum and frontal lobe, including the (A) ventral striatum, (B) insular cortex, (C) midbrain, and (D) ventromedial prefrontal cortex. Supporting Table 1 provides the spatial coordinates of all 14 clusters meeting activation criteria.

activity,<sup>31</sup> these results suggest that medication-induced increases in mesocorticolimbic network activity contribute to clinically manifest ICBs. These

findings also emphasize the utility of CBF measured through ASL as a noninvasive imaging method to localize and evaluate clinically meaningful medication responses.

### The Ventral Striatum and Maladaptive Behaviors

A number of functional imaging studies support our finding that DAgonists induce concerted changes to the ventral striatum and mesocortical network, and that increased ventral striatal blood flow relates to behavioral impulsivity. Given significant levels of D3 receptor expression in the ventral striatum,<sup>5,6</sup> the observed modulation of ventral striatal neural activity by D3 preferring medication is well supported.<sup>5</sup> Examination of analogous compulsive reward-driven behaviors, such as drug addiction and binge eating, emphasize that the mesocorticolimbic network differs in patients who exhibit compulsive participation in reward-driven behaviors.<sup>32,33</sup> Rodent studies of addiction illustrate similar ventral striatal CBF increases as a result of cocaine administration.<sup>34</sup> In humans, ventral striatal CBF increases are manifest after dosing with drugs of addiction,<sup>35</sup> associated with cravings among patients suffering from addiction,<sup>36</sup> and present in response to rewarding<sup>37</sup> and novel<sup>38</sup> stimuli. Taken together, DAgonist treatment may result in increased resting-state mesocorticolimbic network activity reflected by increased ventral striatal CBF, thus accounting for the increased association of ICBs with this medication class.

### Ventral to Dorsal Striatum Networks: The Transition to Compulsivity

The CBF increase in response to DAgonist was not restricted to the ventral striatum, but included modulation of dorsal striatal networks. Voxel-based analysis showed increased CBF in the midbrain (SN+periaqueductal gray matter), ventromedial prefrontal cortex (vmPFC), insular cortex, and striatum. Past evidence links cortical-dorsal striatal networks to repetitive behaviors and compulsive habit formation, and the ventral striatum to limbic areas and emotionally valent behaviors.<sup>39</sup> Consequently, both components of the striatum are individually implicated in separate aspects of repetitive, rewarding patterns of behavior.<sup>39,41</sup> Although dorsal and ventral striatal circuits are largely segregated, information may be transferred between them through the SN, through the striato-nigro-striatal system.<sup>42,43</sup> This feed-forward mechanism is structured as an ascending spiral, in which populations of striatal neurons interface with adjacent subregions by way of dopaminergic midbrain cells, gradually moving from ventral to dorsal domains.<sup>42</sup> In this way, parallel information streams from reward, cognitive, and motor control circuits

converge, granting the striato-nigro-striatal tract a significant role in reward learning and habit formation, which are distinctively altered in ICBs.<sup>28,43-45</sup> These findings suggest that drug-induced increases in metabolic activity throughout the striato-nigro-striatal circuit may be an effect of DAgonist administration.

This pattern of aggregate circuit activity may also extend into the cortical components of the frontostriatal tract, indicated by the finding that voxel-wise analysis showed increased CBF in the vmPFC. Previous literature has implicated the vmPFC in processes of valuation and reward-guided behavior, two cognitive mechanisms that operate abnormally for individuals with ICBs.<sup>45-47</sup> The vmPFC is also secondarily associated with the striato-nigro-striatal network, because it projects to the ventral striatum and exerts cognitive control over behavior.<sup>46</sup> This evidence further emphasizes the possibility of broad functional network alterations in generating ICBs. However, the greater implications for an integrative circuit-based approach remain to be determined. Whether this hyperactivity is associated with concerted corticostriatal network activity is not yet known.

### Contrast to Findings Reporting Decreased CBF

We note that in contrast to this work, Black and colleagues (2002) conducted a study of acute DAgonist administration in nonhuman primates, and concluded that this class of medication decreased CBF in the ventral striatum.<sup>48</sup> However, a concern arises regarding the sedation of primate subjects, because anesthesia has been observed to decrease ventral striatal CBF in sedated animals, with an increase in activity occurring in awake animals.<sup>49</sup> Furthermore, this study was conducted using healthy monkeys rather than a Parkinsonian model.

Few studies have assessed the influence of DAgonist on CBF in PD-ICB patients. In one study,<sup>15</sup> <sup>15</sup>O PET was administered to a small cohort of PD participants performing a gambling task, and ICB<sup>+</sup> patients demonstrated a significant CBF decrease from an *off*- to *on*-apomorphine state in the lateral orbitofrontal cortex, rostral cingulate, amygdala, and external pallidum.<sup>50</sup> Although apomorphine is a D1- and D2-like receptor agonist, it is infrequently associated with the development of ICBs in clinical populations. The current study examined patients utilizing commonly prescribed DAgonists, (i.e., ropinirole or pramipexole), implicated as a primary cause for development of ICBs.<sup>51</sup> These compounds have a distinct pharmacological profile, with low affinity for D1, and higher affinity for D2-like receptors.<sup>5</sup> Therefore, it is not surprising that we observe a dissimilar CBF response using more conventionally prescribed DAgonists compared to apomorphine. Studies that address the impact

of L-dopa or D1 agonists on CBF would further clarify how dopaminergic modulation alters dorsal versus ventral striatal networks.

One other study<sup>10</sup> reported decreased ventral striatal CBF in ICB<sup>+</sup> patients *on*-dopamine therapy (including L-dopa), while utilizing ASL methods similar to those used here. A study design difference is apparent in that subjects in Rao and colleagues (2010) remained in the *on*-dopamine state for the duration of the experiment, whereas subjects in the present study were scanned both in an *on*-DAgonist and *off*-DAgonist state. The present results therefore emphasize the acute response to DAgonists, whereas the approach taken by Rao and colleagues (2010) does not allow for the disentanglement of baseline differences from either acute or prolonged exposure to DAgonists. Contrasting technical parameters also contribute to CBF differences, notably through labeling duration and PLD values (2,000 ms/1,000 ms, respectively, in the former study; 1,500 ms/1,500 ms in the current study). Short PLD times (<1,500 ms) can produce vascular artifacts in patients with normal neurovasculature attributed to insufficient time allowed for complete exchange of labeled blood water with tissue water,<sup>52</sup> potential causing an increased signal attributed to the combination of blood volume artifact and some perfusion signal.

This study should also be considered in light of several limitations. First, we utilized a pCASL PLD = 1,500 ms to match that of other recent multicenter trials that utilize pCASL.<sup>53</sup> However, a recent guidelines paper from the ISMRM perfusion study group suggests that a PLD = 2,000 ms may be more appropriate. This recommendation is based on potential cerebrovascular disease in older subjects and lengthened bolus arrival times. Given that our patients did not have clinical indicators of cerebrovascular disease, we believe that PLD = 1,500 ms is likely sufficiently long to allow for exchange of labeled blood and tissue water, and thus we have inspected our data for residual intraluminal signal, which was not observed. Also, because this study focuses on medication-induced CBF changes, and there is no evidence that DAgonist alters bolus arrival times, it is unlikely that this PLD choice represents a major confound. Second, we did not administer other measures of nonmotor PD symptoms (e.g., UPDRS part I or apathy assessments), thus limiting interpretation to other potential psychiatric comorbidities. Finally, the sample size was relatively small and did not allow for some potential covariates to be evaluated in the main analysis of subcortical ROIs. However, bivariate analyses comparing the association between demographic parameters with CBF did not find any significant relationships, and the post-hoc ANCOVA showed that ventral striatal differences were preserved while including seven potential confounding factors.

## Conclusions and Future Directions

While noninvasive MRI modalities capable of assessing CBF, such as pCASL, present clinically feasible methods for quantitative analysis of medication effects, it is also necessary to relate CBF to underlying neuronal function in ICB patients. This is especially crucial in extrastriatal regions. Additionally, it is unclear how neuronal changes evolve in PD patients prone to developing DAgonist-induced ICB, because the participants of the present study were likely affected by extensive exposure to DAgonist therapy. Thus, these findings may be more reflective of modification attributed to long-term treatment, rather than an inherent vulnerability to DAgonists. Therefore, a longitudinal study seeking to image PD patients over the course of DAgonist therapy is necessary. If CBF imaging following acute DAgonist administration can be used to predict vulnerability to DAgonist-induced ICBs in de novo PD patients, it would emerge as a tool of great clinical utility, allowing for screening and subsequent personalization of medication regimens to avoid negative outcomes. Overall, these findings emphasize a clear link between medication-induced, reward-driven behaviors and medication-induced CBF changes to key reward-based networks in PD. It extends previous imaging studies in ICB by linking clinical severity to acute DAgonist administration and concerted functional changes in key mesocorticolimbic structures. ■

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## Supporting Data

Additional Supporting Information may be found in the online version of this article.