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[¹⁸F] AV-1451 uptake in corticobasal syndrome: the influence of beta-amyloid and clinical presentation

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Abstract

Corticobasal syndrome (CBS) is a phenotypic manifestation of diverse pathologies, including Alzheimer's disease and 4-repeat tauopathies. Predicting pathology in CBS is unreliable and, hence, molecular neuroimaging may prove to be useful. The aim of this study was to assess regional patterns of uptake on [¹⁸F] AV-1451 PET in CBS and determine whether patterns of uptake differ according to beta-amyloid deposition or differing clinical presentations. Fourteen patients meeting criteria for CBS underwent Pittsburgh Compound B (PiB) and [¹⁸F] AV-1451 PET. Seven patients presented as CBS and seven presented with apraxia of speech (AOS) and later evolved into CBS. A global PiB summary was calculated and used to classify patients as PiB (–) or PiB (+). AV-1451 uptake was calculated in fourteen regions-of-interest, with values divided by uptake in cerebellar crus grey matter to generate standard uptake value ratios. AV-1451 uptake was considered elevated if it fell above the 95th percentile from a group of 476 cognitively unimpaired normal controls. Six of the 14 CBS patients (43%) were PiB (+), with three of these patients showing strikingly elevated AV-1451 uptake across many cortical regions. Of the eight PiB (–) patients, only those with AOS showed elevated AV-1451 uptake in supplementary motor area and precentral cortex compared to controls. No region of elevated AV-1451 uptake were observed in PiB (–) typical CBS patients without AOS. These results suggest that regional [¹⁸F] AV-1451 is variable in CBS and depends on the presence of beta-amyloid as well as clinical presentation such as AOS. PiB (+) CBS does not necessarily reflect underlying Alzheimer's disease; however, the possibility some of these patients will evolve into Alzheimer's disease over time cannot be excluded.

Keywords

corticobasal syndrome; Alzheimer's disease; tau; beta-amyloid; positron emission tomography

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All authors report no conflict of interest.

Introduction

Corticobasal syndrome (CBS) is a clinical phenotype typically characterized by asymmetric progressive rigidity, bradykinesia, dystonia, ideomotor apraxia and myoclonus [1], with atrophy observed in the supplementary motor, premotor, parietal and superior frontal cortex [36]. It has also been recognized that subjects can first present with the motor speech disorder, apraxia of speech (AOS) [17, 19] which may then later evolve into CBS. Apraxia of speech is characterized by slow speaking rate, abnormal prosody, distorted sound substitutions, additions, repetitions and prolongations, and syllable segmentation [7, 10], and has been associated with atrophy in the supplementary motor and premotor regions [18]. It is therefore not surprising that over time AOS could evolve into CBS. Underlying neuropathology of CBS is highly variable, including Alzheimer's disease, corticobasal degeneration, progressive supranuclear palsy, and frontotemporal lobar degeneration with TAR DNA binding protein of 43 kDa [2, 24]. Clinical prediction of underlying pathology is unfortunately unreliable [12, 32]. Clinical criteria have been developed for CBS [1], but they fall short of providing clinical features predictive of CBD pathology, and hence have low diagnostic specificity. Hence, CBS should be thought of as a highly heterogeneous clinical condition, the etiology of which can thus far only be ascertained with post mortem pathological exam.

Molecular positron emission tomography (PET) imaging has the potential to provide insight into the underlying proteinopathy during life. PET ligands, such as Pittsburgh Compound B (PiB)[23], are available that can detect the presence of beta-amyloid in the brain, and hence provide a presumed marker of Alzheimer's disease. The recent development of PET ligands for the protein, tau, also provide a promising avenue for diagnosing pathology in CBS. One such ligand is [^{18}F]AV-1451 [38] which has been shown to bind avidly to tau proteins with paired helical filament conformation and a mix of 3 repeat and 4 repeat tau isoforms, such as that seen in Alzheimer's disease [26, 28, 31, 38]. Patients with Alzheimer's disease show elevated AV-1451 uptake in the entorhinal cortex early in the disease, spreading to inferior temporal, lateral parietotemporal, precuneus, amygdala and fusiform cortices [3, 5, 15]. The role of [^{18}F] AV-1451 in 4 repeat tauopathies, such as corticobasal degeneration and progressive supranuclear palsy, is less clear. Autoradiographic studies have suggested little, or no, binding of [^{18}F] AV-1451 to 4-repeat tau proteins in these diseases [20, 26, 28, 31]. In addition, "off-target" binding of [^{18}F] AV-1451 has been observed in the elderly population in several regions that complicates the interpretation of the [^{18}F] AV-1451 PET scans in these diseases [6, 26]. Despite these issues, however, a couple of studies have shown good regional correlations between tau burden at autopsy and [^{18}F] AV-1451 uptake on PET in corticobasal degeneration [20, 29]. There is no significant binding to TDP-43 and alpha-synuclein [26, 28, 31].

A few studies have reported [^{18}F] AV-1451 tau PET findings in CBS patients, with elevated uptake observed in precentral and postcentral cortex, superior frontal and parietal lobe, and basal ganglia [4, 20, 22, 29, 33]. Elevated [^{18}F]AV-1451 has also been observed in the supplementary motor area in one CBS subject with AOS [20]. However, no studies have systematically assessed the influence of the presence of beta-amyloid deposition, or the presence of clinical presentation, such as AOS, on the patterns of tau uptake in CBS. It is

therefore unknown whether all CBS subjects with beta-amyloid deposition will show tau-PET findings consistent with Alzheimer's disease, and it is also unknown whether clinical presentation influences the patterns of tau deposition. In this study, we utilize data from a large age matched normal control population to assess [^{18}F] AV-1451 tau-PET findings in CBS and to better understand the relationships with clinical presentation and with beta-amyloid via PiB-PET.

Methods

Patients

All patients were recruited from the Department of Neurology, Mayo Clinic, and were evaluated by a neurodegenerative disease expert (KAJ). Fourteen patients that met clinical criteria for CBS [1] were recruited into the study and underwent Pittsburgh compound B (PiB) PET for beta-amyloid quantification, [^{18}F] AV-1451 tau PET, and a 3T volumetric head MRI. Of these 14 CBS patients, seven initially presented with isolated progressive AOS and then, over years, evolved into CBS. All 14 underwent prospective standardized neurological tests to assess for global cognitive function (the Montreal Cognitive Assessment Battery (MoCA)) [30], executive function (the Frontal Assessment Battery (FAB)) [9] and motor signs of Parkinsonism (the Movement Disorders Society sponsored revision of the Unified Parkinson's Disease rating scale part III (MDS-UPDRS III) [11]), as well for the presence or absence of limb dystonia, myoclonus, ideomotor apraxia and alien limb phenomenon. No patient responded to levodopa/carbidopa treatment.

All participants provided written consent and the study was conducted with approval of the Mayo Clinic Foundation Institutional Review Boards.

PET analyses

All PET scans were acquired using a 690 XT PET/CT scanner (GE Healthcare, Milwaukee, Wisconsin) operating in 3D mode. For tau-PET, an intravenous bolus injection of approximately 370MBq (range 333–407 MBq) of [^{18}F] AV-1451 was administered, followed by a 20-minute PET acquisition performed 80 minutes after injection. For PiB-PET, subjects were injected with PiB of approximately 628 MBq (range, 385–723 MBq) and after a 40–60-minute uptake period a 20 minute PiB scan was obtained consisting of four 5-minute dynamic frames following a low dose CT transmission scan. Emission data was reconstructed into a 256×256 matrix with a 30-cm FOV (Pixel size=1.0mm, slice thickness=1.96mm). All subjects had a 3T magnetization prepared gradient echo (MPRAGE) sequence performed within 1–2 days of the tau-PET, as previously described [13].

All PET scans were co-registered to each subject's MPRAGE using SPM and the automated anatomical labeling atlas[35] was transformed into the native space of each MPRAGE in order to calculate regional data. For PiB-PET, a global standard uptake value ratio (SUVR) was calculated as previously described [13]. Briefly, median uptake in prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus regions were calculated and divided by median uptake in the cerebellar crus grey matter. The

global SUVR was generated by combining uptake ratios from the six regions. A subject was considered beta-amyloid positive if the global PiB SUVR was >1.42 [14]. For tau-PET, we calculated tau uptake across fourteen regions of interest (ROIs). The bilateral superior frontal, superior parietal, precentral, supplementary motor and thalamus ROIs were selected because they are typically involved in CBS and/or AOS. Bilateral inferior temporal and entorhinal cortex were included because they have been shown to be some of the earliest regions with elevated tau uptake in Alzheimer's disease. To create standard uptake value ratios (SUVRs), tau-PET uptake in each ROI was divided by uptake in cerebellar crus grey matter. Grey matter plus white matter sharpening in both target and reference regions and partial volume correction were used to generate SUVRs. A similar signal was seen without partial volume correction.

Statistical analysis

Four hundred seventy-six clinically unimpaired participants between the ages of 50 and 85 without amyloidosis based on PiB PET SUVR values less than 1.42 were selected to serve as a control group. In order to obtain normal ranges of AV-1451 PET for a given age, we used this control group to fit linear regression models of log AV-1451 PET SUVR versus age within each region and created 95% prediction intervals. These prediction intervals show the range of expected AV-1451 PET values for a clinically unimpaired amyloid negative patient at a given age. The AV-1451 PET values of 14 CBS cases were plotted versus age and superimposed on the prediction intervals to assess abnormality.

We performed a second focused analysis within the precentral and supplemental motor area, regions expected to be affected in AOS cases. Fisher's exact test was used to determine independence of association between AOS or PiB positive status and AV-1451 uptake higher than 97.5% of controls in either hemisphere. We then used simple linear regression to obtain effect estimates with confidence intervals for the association between AOS positive status and AV-1451 uptake while controlling for PiB uptake (as a continuous predictor) and age-at-scan. All statistical analyses were performed using the statistical software R[34] (version 3.4.1).

Results

Patient demographics and clinical data are summarized in tables 1 and 2. A total of six of the 14 CBS patients were PiB-PET positive, two of whom had presented with AOS whereas the remaining four were AOS negative. All patients had limb apraxia and rigidity ($n=14$) and a majority had limb myoclonus ($n=10$), and limb dystonia ($n=9$) while a minority had an alien-limb phenomenon ($n=3$). The cohort had a median disease duration of 3 years (range 1–10 years), median UPDRS III score of 44 (range 27–81), median FAB scores of 10 (range 0–17), and median MoCA score of 20 (range 7–27). The AOS positive patients tended to have longer disease duration and perform poorer on the MoCA, FAB and UPDRS-III compared to the AOS negative patients (Table 2). The PiB (+) patients tended to have more myoclonus (83% vs 62%) compared to the PiB (–) patients. One of the CBS PiB (–) patients (subject 7) has died with autopsy proven corticobasal degeneration [40].

The regional tau-PET SUVRs in the 14 patients are compared to the range of values observed in the 476 cognitively normal subjects in Figure 1. These are stratified by dominant (more affected by disease) and non-dominant hemisphere. The tau-PET scan from each of the fourteen patients in the study and an age matched PiB negative control are shown in Figure 2. Of the six PiB (+) CBS patients, three showed AV-1451 uptake greater than the range seen in normal subjects across all regions except for the thalamus. Two of these PiB (+) patients showed striking uptake throughout the cortex (patients 3 and 5, Figure 2) and one showed striking uptake restricted to premotor and motor cortices (patient 1, Figure 2). The remaining three PiB (+) patients did not show any evidence for elevated tau uptake compared to controls.

The only regions in which PiB (–) CBS patients showed elevated tau compared to controls were the supplementary motor area, precentral cortex and superior frontal cortex. The PiB (–) CBS patients that showed elevated tau in these regions all presented with AOS. In fact, all the patients with AOS showed tau uptake in the upper normal range or above the normal range in the supplementary motor area and precentral cortex. None of the PiB (–) patients without AOS showed tau uptake outside the range of normal controls in any region.

To determine the significance of this association a Fisher's exact test was performed on the contingency table shown as table 3. AOS positive or PiB positive status was found to be associated with elevated [^{18}F] AV-1451 uptake in regions we expect to be affected in AOS ($p=0.03$); the precentral and supplemental motor area in either hemisphere. Of eleven cases that were AOS or PiB positive, nine had tau above the normal control range in at least one region and hemisphere (in this sample, AOS or PiB positive patients were 4.5 times more likely to have elevated tau in at least one region). Three cases that were both AOS and PiB negative had tau well within the normal control range.

We performed four simple linear regressions (table 4), one in each region and hemisphere we expect to be associated with AOS (precentral and supplemental motor area), to obtain estimates of the effect of AOS positive status on [^{18}F] AV-1451 uptake while controlling for PiB (as a continuous variable) and age-at-scan. In every region, there was a greater than 20% increase in uptake associated with AOS positive status. The only significant p-value (less than 0.05) was in the precentral left hemisphere, but all p-values were “low” when considering the sample size. This indicates that there is likely an association between AOS positive status and [^{18}F] AV-1451 uptake in these regions.

Discussion

In a field of rapidly evolving molecular imaging, and increasing use of tau protein ligands, this study contributes important data on [^{18}F] AV-1451 binding characteristics in CBS. Our data showed that while over a third of CBS patients were positive for beta-amyloid not all patients with beta-amyloid deposition showed AV-1451 characteristics typical of Alzheimer's disease. With that said, AV-1451 uptake was only strikingly elevated in CBS in the presence of beta-amyloid deposition, or focally in the SMA and precentral gyrus when AOS was the initial presentation.

It was not surprising that over a third of the CBS patients in our study had PiB SUVR values consistent with beta-amyloid being present in the brain. What was surprising was the fact that only half of the PiB (+) CBS patients showed elevated AV-1451 uptake, with two of the six showing widespread cortical uptake patterns typical of those observed in Alzheimer's disease. One other patient also showed striking AV-1451 uptake but in a more focal pattern affecting the premotor and precentral cortex; this case also had AOS. The remaining three PiB (+) patients did not show patterns of uptake consistent with Alzheimer's disease. This may suggest that beta-amyloid deposition in these latter patients may instead reflect diffuse plaques consistent with pathological aging. Of four PiB(+) patients that have previously been reported in three previous studies [22, 33, 37], one patient similarly did not show any evidence for elevated ligand uptake [22], although this study used the [^{18}F]THK-5351 ligand.

The PiB (–) patients with CBS who did not have AOS did not have elevated uptake in any region seen on [^{18}F] AV-1451 PET scans when compared with controls. This contrasts with multiple prior reports of elevated tau-PET SUVRs in CBS, most notably in certain anatomic regions thought to be responsible for symptoms, including premotor, motor, supplementary motor cortex, as well as basal ganglia and thalamus. Three clinical series compared [^{18}F] AV-1451 uptake in CBS with normal controls and other tauopathies, and reported elevated SUVRs in precentral, postcentral, superior parietal cortices, basal ganglia and thalamus [4, 22, 33]. The reports are however limited by a small control population. In our study we used a very large control population of almost 500 patients. In addition, given the absence of pathological confirmation, we cannot exclude the possibility that different pathologies may be underlying the CBS in theirs and our studies. TDP-43 pathology, for example, can account for CBS, and TDP-43 appears to be associated with increased uptake of AV-1451 predominantly in white matter especially in regions with the most atrophy [27, 39]. In addition, off-target binding of [^{18}F]AV-1451 has been reported in deep grey matter structures perhaps secondary to iron accumulation [6] and could account for differences. Our findings are in line with prior reports that include post-mortem autoradiographic evaluation of [^{18}F] AV-1451 showing little to no significant binding to 4R tau-isoforms such as those seen in corticobasal degeneration [20, 26].

The presence of AOS as a presenting feature showed a trend towards higher AV-1451 SUVR values above the range of normal controls, particularly in the supplementary motor area and precentral cortex. This is a novel finding and has not been described previously. These regions also typically show atrophy and hypometabolism on MRI and FDG-PET in patients with AOS [17, 18]. There are many possible explanations for the elevated uptake in the patients with AOS. It may suggest that patients with AOS have a higher tau burden in these regions compared to CBS patients without AOS. While no autopsy studies have compared CBS patients with and without AOS, one study assessing patients with progressive supranuclear palsy found more 4R tau pathology in neocortical regions of patients with AOS compared to those without AOS [16]. It is therefore possible that we are seeing a similar shift in 4R tau pathology in CBS when it presents with AOS. Given the uncertainty however over whether AV-1451 is binding 4R tau, it is also possible that the findings reflect a greater degree of neurodegeneration, i.e. neuronal cell loss, gliosis, or neuroinflammation, in premotor and precentral cortices in patients with AOS as these neurodegenerative processes

are observed in corticobasal degeneration [21, 25]. It is less likely that there is more paired helical filament or mixed 3+4R Alzheimer's type tau in these regions in CBS cases with AOS, as a pathological case study of CBS with AOS showed only 4R tau in these areas [20]. Previous clinicopathological studies have also indicated that apraxia of speech is predominantly associated with 4R tau pathology [8, 16, 17]. Until we understand the nature of the [^{18}F] AV-1451 uptake in 4R tauopathies these possible explanations remain speculative. AOS was associated with elevated AV-1451 PET SUVRs, even in PiB negative patients, however to assess whether this clinical feature is predictive of a non-Alzheimer's tauopathy, the study will need to be replicated with a larger sample. The patients with AOS showed longer disease duration compared to those without AOS which may also be playing some role in the degree of uptake. However, we still observed elevated uptake in subject 2 that had disease duration of only 1.5 years.

One of the strengths of this study is that our normal control population consisted of almost 500 patients. A limitation of this study is lack of pathologic confirmation of the diagnosis, making results of [^{18}F] AV-1451 uptake difficult to interpret with certainty; only patient 7 had a pathological confirmation of corticobasal degeneration. Our relatively small number of CBS patients also limited our ability to perform more complex analyses across patients with and without beta-amyloid deposition or AOS. Nevertheless, our cohort provided invaluable information concerning variability in [^{18}F] AV-1451 tau-PET uptake in CBS, and our findings will have important implications for the interpretation of beta-amyloid PET scans in CBS patients and for future trial designs that involve CBS patients.

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Figure 1:

AV-1451 PET SUVR versus age-at-scan by region and dominant/non-dominant hemisphere, with dominant hemisphere defined as the opposite hemisphere of the limb/side of greater motor/sensory impairment. Each patient is represented by a different number. The left two columns show the data by AOS positive versus negative status. The right two columns show the same data by PIB positive versus negative status. High values on the vertical axis have been compressed to better show the data. The shaded band is derived from a linear regression model among clinically normal individuals and is drawn to cover approximately 95% of the normal population.

Figure 2:

[18F] AV-1451 tau PET scans from CBS patients 1–14 and a normal control. PET scans are shown as standard uptake value ratio images, where uptake in all voxels was divided by uptake in the cerebellar crus grey matter. Slices were taken in subject space to illustrate supplementary motor, premotor, entorhinal, superior parietal cortices, hippocampus and cerebellar crus. Anatomical left is on the left side of the image.

Table 1:

Demographics and disease characteristics of the fourteen CBS cases. Individuals are organized by PiB/Amyloid status.

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14
AOS status	Positive	Positive	Negative	Negative	Negative	Negative	Positive	Positive	Positive	Positive	Negative	Negative	Negative	Positive
PiB/Amyloid status	Positive	Positive	Positive	Positive	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Handedness	Right	Right	Right	Right	Right	Left	Right	Right	Right	Right	Right	Right	Right	Right
Gender	Female	Male	Female	Female	Male	Male	Male	Male	Male	Male	Male	Female	Female	Male
Age at diagnosis	68	76	53	61	62	71	58	66	67	82	60	63	65	58
Age at first clinical symptom	50	74	49	55	60	69	49	63	59	72	58	60	62	55
Illness duration	4	1.5	2	6	2	1	9	4	8	10	2	3	1	3
Global PiB	1.82	2.00	2.08	1.53	1.99	2.01	1.18	1.23	1.36	1.32	1.35	1.34	1.21	1.39
MoCA *	22	9	13	NA	23	29	7	20	NA	18	27	NA	27	8
FAB **	15	1	8	NA	10	NA	0	10	NR	NR	17	NA	17	7
MDS-UPDRS-III ***	59	80	28	NR	27	32	72	44	43	81	27	NR	28	48
Limb rigidity or akinesia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Limb dystonia	Yes	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Limb apraxia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Limb myoclonus	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	Yes
Alien Limb phenomenon	Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No
Side of motor predominance	Right	Right	Left	Right	Left	Right	Left	Left	Right	Right	Left	Left	Left	Right

* MoCA = Montreal Cognitive Assessment

** FAB = Frontal Assessment Battery

*** MDS-UPDRSIII = Movement Disorders Sponsored Unified Parkinson's Disease Rating Scale III

NA= Not able to complete the test due to patient not being able to complete components of the examination

NR = not all components recorded

Table 2:

Demographic and clinical summaries over all, by AOS status, and by PiB status. Categorical variables are summarized as number (%) and continuous variables are summarized as median (range).

Variable	Total (n=14)	AOS- (n=7)	AOS+ (n=7)	PiB- (n=8)	PiB+ (n=6)
Male sex	9 (62%)	3 (43%)	6 (86%)	6 (75%)	3 (50%)
Illness duration, yrs.	3 (1, 10)	2 (1, 6)	4 (1.5, 10)	4 (1, 10)	2 (1, 6)
Right handedness	13 (93%)	6 (86%)	7 (100%)	7 (100%)	5 (83%)
MoCA *	20 (7, 27)	27 (13, 29)	14 (7, 22)	19 (7, 27)	22 (9, 29)
FAB **	10 (0, 17)	14 (8, 17)	7 (0, 15)	10 (0, 17)	9 (1, 15)
MDS-UPDRSIII ***	44 (27, 81)	28 (27, 32)	59 (43, 81)	44 (27, 81)	32 (27, 80)
Limb rigidity, yes	14 (100%)	7 (100%)	7 (100%)	8 (100%)	6 (100%)
Limb dystonia, yes	9 (64%)	5 (71%)	4 (57%)	6 (75%)	3 (50%)
Limb apraxia, yes	14 (100%)	7 (100%)	7 (100%)	8 (100%)	6 (100%)
Limb Myoclonus, yes	10 (71%)	4 (57%)	6 (86%)	5 (63%)	5 (83%)
Alien-Limb	3 (21%)	0 (0%)	3 (43%)	1 (13%)	2 (33%)
Right motor predominance	7 (50%)	2 (29%)	5 (71%)	3 (38%)	4 (67%)

* MoCA = Montreal Cognitive Assessment

** FAB = Frontal Assessment Battery

*** MDS-UPDRSIII = Movement Disorders Sponsored Unified Parkinson's Disease Rating Scale III

Table 3:

A contingency table of AOS positive and/or PiB positive vs both AOS and PiB negative status by elevated uptake in either hemisphere of the precentral or SMA vs neither hemisphere in either region elevated above 97.5% of controls of the 14 CBS cases.

	Any precentral or SMA hemisphere uptake >97.5% of normal controls	All precentral and SMA hemisphere uptake < controls
AOS+ and/or PiB+	9	2
AOS- and PiB-	0	3

Fisher's exact test for the above table – p-value=0.027

Table 4:

Estimates of association between AOS positive status and [^{18}F] AV-1451 uptake in both hemispheres of the precentral and supplemental motor area after adjusting for PiB uptake (continuous) and age-at-scan from four simple linear regressions.

Region	Hemisphere	Change (% increase) in uptake associated with AOS positive status	95% confidence interval	Unadjusted p-value	FDR corrected p-value
Precentral	Left	40.7	(12.8, 68.6)	0.009	0.037
Precentral	Right	28.4	(−5.5, 62.3)	0.091	0.121
Supplemental Motor Area	Left	21.0	(−3.7, 45.6)	0.086	0.121
Supplemental Motor Area	Right	23.3	(−9.0, 55.7)	0.137	0.137

FDR: False discovery rate.