Basal ganglia and language: phonology modulates dopaminergic release

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Abstract

The basal ganglia have been implicated in syntactic and phonological processes, but direct evidence has been scarce. Here, we used (^{11}C)Raclopride and Positron Emission Tomography (PET) to measure modulations of the dopaminergic system induced by phonological or syntactic processing. Two significant effects were found. First, the level of accuracy in phonological processing significantly correlated with tracer binding potential in the left caudate nucleus. Second, the speed in phonological processing significantly correlated with tracer binding potential in the left putamen. Thus, a more accurate and fast phonological processing was associated with a reduced dopamine requirement in the left striatum. These findings show that the striatal dopaminergic system plays an essential role in grammatical processes that form the core of human language.

Keywords: PET; Dopamine; Caudate; Putamen; Language; Phonology; Syntax.

Introduction

Strong evidence for a role of basal ganglia in cognition has come from research in primates, showing that the basal ganglia are interconnected by input and output fibers with the frontal lobe [1]. It has now become clear that cortico-subcortical pathways involving the basal ganglia underlie many cognitive capacities (e.g. [2]).

Recent findings implicate the basal ganglia in human language. We have previously reported a PET study in which the neural correlates for different grammar components (i.e. syntax, morphosyntax and phonology) were carefully disentangled by eliminating the access to lexical-semantics [3]. Syntactic processing selectively activated Broca's area, the left insular cortex and, notably, the left caudate nucleus. Similar findings regarding the left caudate nucleus were obtained in a fMRI study on syntactic processing [4].

Different accounts for the role of basal ganglia in syntactic processing have been proposed. Ullman [5] proposed that a fronto-striatal procedural system subserves the use of recursive compositional principles governing the assembling of morphemes and phonemes into higher order units such as words, phrases and clauses. This procedural system underlies syntax and other grammatical aspects such as phonology [5,6]. Friederici [7] proposed that the basal ganglia play a role in controlled syntactic reanalysis that is necessary when lexical-semantics cannot be integrated into preliminary syntactic structures. This process seems to be defective in patients with basal ganglia cerebrovascular lesions [8].

Degenerative diseases affecting the nigrostriatal dopaminergic system have been associated with deficits in syntactic and phonological processing. About half of non-demented patients with Parkinson's Disease (PD) seem to be impaired in the comprehension of syntactically complex sentences (e.g. [9]). Output phonological processing (phonemic encoding and prosody) may also be damaged in PD patients (e.g. [10]).

Thus, several lines of research converge in suggesting that the basal ganglia play a

role in grammatical processing. Here, we tested this hypothesis *in vivo* using (^{11}C)Raclopride and PET [11] in healthy subjects, by investigating modulations of dopamine binding to D2 receptors induced by phonological and syntactic processing. As in most recent studies of neurotransmission in cognition (e.g. [12]), a closely matched control condition, with similar sensorimotor and cognitive demands but no linguistic processing, was also included.

Methods

Subjects

8 healthy right-handed male subjects (mean age 24.5 years, range 22-29 years) of comparable education level (University students) participated in the study. All were native monolingual speakers of Italian, with no history of neurological or psychiatric disorders. They gave written consent to participate in the study after receiving an explanation of the procedures, in conformity with the Declaration of Helsinki. The study was approved by the local Ethics Committee (San Raffaele Hospital, Milano).

Experimental design

The experimental design was adapted from our previous study [3]. Subjects were scanned in 3 different sessions, at intervals of approximately 1 week. In each session, a single (^{11}C)Raclopride PET scan was acquired, whilst subjects were administred one of 3 different tasks: A) Detection of phonological anomalies (Ph); B) Detection of syntactic anomalies (Syn); C) A closely matched baseline condition (Bsl) controlling for ocular movements, motor response, symbol recognition, and decision making. In Ph and Syn, subjects were presented with sentences made with pseudowords (pseudosentences), so as to eliminate the access to lexical-semantics. On the one hand, the phonology, functional morphemes, and grammatical rules of the native language (Italian) were maintained. On the other hand, anomalies either at the phonological (condition Ph) or the syntactic (condition Syn) level were introduced. Phonological anomalies presented pseudosentences containing unlegal consonant strings, whereas syntactic anomalies presented pseudosentences with wrong linear order but proper agreement.

Examples:

Phonological anomalies: * "Il gulco gianigzleva le brale."

($Art_{m/s}$ $N_{m/s}$ V(Ph-anomaly)-T/$AGR_{past/3rd\ s}$ $Art_{f/p}$ $N_{f/p}$)

Ph-anomaly = [gzl], unlegal string of consonants in Italian.

Equivalent for an English speaker to: * "The gongstrz walched." containing unlegal strings such as [ngstrz].

Syntactic anomalies: * "Gulco il gianigeva le brale."

($N_{m/s}$ $Art_{m/s}$ (Syn-anomaly) $V\text{-}T/AGR_{past/3rd\ s}$ $Art_{f/p}$ $N_{f/p}$)

Syn-anomaly = wrong word order: N precedes Art.

Equivalent for an English speaker to: * "Gongle walched the." as opposed to "The gongle walched."

Glosses: $Art_{(gender/number)}$ = article; $N_{(gender/number)}$ = noun; $V\text{-}T/AGR_{(tense/agreement)}$ = verb; m =masculine; f = feminine; s = singular; p = plural.

Correct and anomalous pseudosentences were presented in random order. Subjects were required to press a response key with the right hand only in case a sentence was correct.

The Bsl consisted of stimuli formed by 5 symbols uniformly ordered on a horizontal line. Stimuli consisting either of only crosses or of 4 crosses and a square were presented in random order. If present, the square could be placed at any of the 5 horizontal positions. Subjects were required to press a response key just in case a stimulus contained only crosses.

The proportion of target (response required) and non-target stimuli was 4:9 for all conditions. Each stimulus was presented for 4000 ms, followed by a 1000 ms interval. A single series of 520 stimuli was presented, with a 10 s pause every 52 stimuli. Task adminstration began 120 s before tracer injection and lasted for 45 minutes. The order of the 3 tasks was counterbalanced across subjects. Reaction times (RT) and response accuracy (Acc) were recorded for each subject.

PET data acquisition

Data were acquired with a GE-Advance 3D scanner (General Electric Medical System, Milwaukee, WI), with an axial FOV of 15.2 cm, in list mode (event-by-event), with

post acquisition frame re-binning, resulting in the dynamic sequence: 4*60s, 3*120s, 10*300s time-frames (Total 60 minutes). Trans-axial images were reconstructed using a Shepp-Logan filter (cut-off 5 mm filter width) in the transaxial plane, and a Shepp-Logan filter (cut-off 8.5 mm) in the axial direction. Images were corrected for decay and attenuation by means of a 10-minute transmission scan performed prior to radioligand injection.

Approximately 250 MBq of (^{11}C)Raclopride (median value 263 MBq, range 118-370 MBq) was injected i.v. as a slow bolus over 20 seconds. The radiochemical purity of injected (^{11}C)Raclopride was > 98%.

Tracer kinetic modeling

Quantitative tracer kinetic modeling was performed using a reference tissue compartmental model [13]. The cerebellum was used as the reference tissue (Fig. 1), and was defined by placing circular (diam. 15 voxels) regions of interest (ROI) on each cerebellar hemisphere. The model allows the estimation of the binding potential (BP). Parametric images of BP for the 1-45 minute scan period were calculated.

Statistical analysis

ROIs were drawn on the basal ganglia of the left and right hemispheres based on a previously described method [14], distinguishing between ventral striatum (VS), dorsal putamen (Put_d) and dorsal caudate (Cau_d). ROIs were defined on coronal slices of the standard Montreal Neurological Institute (MNI)-space T1-weighted MRI, corresponding to a MNI-raclopride template previously described [15]. First, the boundary between VS and dorsal striatum was traced [14]. The outer boundaries of VS, Put_d and Cau_d were easily distinguishable from the adjacent structures. VS was sampled from its anterior boundary to the anterior commissure coronal plane. Cau_d was sampled from its anterior boundary to 2/3 of the length of the body of the caudate. Put_d ws sampled from its anterior to posterior

boundaries. ROI size was kept to a minimum, to avoid partial volume effects. ROIs were then spatially normalized to individual scans with nearest neighbour interpolation by using the transformation parameters obtained by normalizing the raclopride template to each individual ADD-image [16].

Non-parametric statistical tests were used due to non-normal distribution of the BP values. Wilcoxon Signed-Ranks tests were used for the paired comparisons between conditions (Ph vs. Bsl, Syn vs Bsl, Ph vs Syn). Correlations between the two measures of task performance (i.e. Acc and RT) and regional BP values (in all 6 anatomical regions) were performed using Spearman's rank correlation coefficient. These correlations were assessed separately for each experimental condition (Ph, Syn, Bsl). For instance, we correlated Acc in the Ph condition with BP values in the left Cau_d in the Ph condition. We also performed correlations between performance and BP, using differential values (in %) between pairs of experimental conditions. For instance, individual (i.e. for each subject) differences (in %) between Acc in the Ph and the Bsl task were correlated with individual differences (in %) between BP values in the left Cau_d in the Ph and the Bsl task. Finally, we performed correlations between individual differences (in %) in performance (rsp. in BP values) between pairs of experimental conditions and individual BP values (rsp. performance) of each condition. For instance, individual differences (in %) between RT in the Ph and the Syn task were correlated with BP values in the left Put_d in the Ph task.

Results

Behavioral data

All subjects performed with high accuracy. Percentage of correct responses differed significantly between conditions (one-way Anova, F(2,7) = 4.2; P = 0.04). None of the t-test paired comparisons (Bonferroni corrected) reached significance (Syn: mean = 97.5 %, st. dev. = 2.7; Ph: mean = 98.6 %, st. dev. = 1.2; Bsl: mean = 98.9 %, st. dev. = 1.6). RT differed significantly between conditions (one-way Anova, F(2,7) = 31.9; P = 6e-06). Significant t-test paired comparisons (Bonferroni corrected) were between Syn and Bsl, and between Ph and Bsl (Syn: mean = 1463 ms, st. dev. = 269; Ph: mean = 1536 ms, st. dev. = 472; Bsl: mean = 548 ms, st. dev. = 162).

ROI data

Paired comparisons: we found no evidence of a significant change in BP values in the Syn and Ph conditions, neither compared to Bsl, nor in the direct comparisons (P < 0.05, Table 1).

Correlations between performance and BP values: we found two significant effects (P < 0.05). When comparing the Ph condition with Bsl, a significant two-sided positive correlation was found between the individual differences in Acc (in %) and the individual differences in BP values (in %) in the left Cau_d (two-sided Spearman rho = 0.778; P = 0.028). Post-hoc one-sided tests showed that this effect was specific to the Ph condition: the only post-hoc test that reached significance was the correlation between the individual differences in Acc (in %) between Ph and Bsl and the corresponding BP values of Ph (Spearman rho = 0.874; P = 0.007). In other words, the worse the individual Acc in the Ph condition compared to Bsl, the higher the level of dopamine released during the Ph task (Fig. 2A)[1].

[1] An analysis of data distribution in the left Cau_d revealed the presence of a single outlier, i.e. one subject having a difference in % BP values between Ph and Bsl that was more than two standard deviations below the mean value. The analysis was therefore repeated without the outlier subject. Both the two-sided positive correlation (two-sided Spearman rho = 0.775; P = 0.048), and the post-hoc one-sided test

The second significant correlation was found in comparing the Ph and the Syn conditions. The individual differences in RT (in %) significantly and negatively correlated with the individual differences in BP values (in %) in the left Put_d (two-sided Spearman rho = -0.810; P = 0.022). Post-hoc one-sided tests showed that this effect was specific to the Ph condition: the only post-hoc test that reached significance was the correlation between the individual differences in RT (in %) between Ph and Syn and the BP values of Ph (Spearman rho = -0.738; P = 0.046). In other words, the slower the individual RT in the Ph condition compared to Syn, the higher the level of dopamine released during the Ph task (Fig. 2B).

(Spearman rho = 0.847; P = 0.024) were still significant.

Discussion

We conducted a PET experiment to measure the selective displacement of a radioligand from dopamine D2 receptors in syntactic and phonological processing. We found two significant correlations specific to the phonological task, one between Acc and BP values in the left dorsal caudate nucleus, and the other between RT and BP values in the left dorsal putamen.

The significant correlations between performance in Ph and dopamine binding indicate a tight coupling between phonological processing and dopaminergic input to the left dorsal basal ganglia. With better individual performances, less dopamine release seems to be required. This suggests that the individual level of difficulty encountered in Ph specifically modulates the dopaminergic system.

The association of striatal function and phonological processing is not altogether new. In particular, in-depth electrophysiological measurements of linguistic performance in patients with PD with implanted electrodes have attributed a role in phonological processing to the right caudate nucleus [17]. Neuropsychological assessments have revealed phonological deficts in patients with PD [18]. In another study [10], linguistic performance was measured in patients with PD before and after surgical implantation of depth electrodes and consequent electrostimulation of subthalamic nuclei, having a positive effect on striatal neurons. After stimulation, the patients displayed a significant improvement in phonological aspects. However, the latter study is controversial, as two recent PET studies in PD patients did not show any increase of striatal dopamine release after deep stimulation of subthalamic nuclei [19,20]. Altogether, these pieces of evidence provide at best an indirect link between the striatal dopaminergic system and phonological processing. Our data constitute novel direct evidence in support of this hypothesis.

The left Cau_d and the left Put_d correlated each with a different measure of performance in phonological processing. The left Cau_d correlated with Acc, whereas the left Put_d correlated with RT. Acc is more sensitive to cognitive control, whereas RT are

more sensitive to the control of executive procedural aspects. This difference may reflect two distinct aspects of phonological processing: a cognitive aspect in the left Cau_d and an executive aspect in the left Put_d. Indeed, the putamen is strongly connected to primary motor and premotor areas and has been primarily implicated in motor functions, whereas the caudate nucleus hosts afferent and indirect efferent projections to the prefrontal cortex and has been primarily implicated in cognitive functions [21].

Contrary to our predictions, we did not find any significant effects of dopaminergic modulations in the basal ganglia for syntactic processing. About a half of PD patients are found to be impaired in syntactic comprehension (although some authors hold that purely syntactic processes may be spared in PD patients, e.g. [22]). In addition, our previous PET activation study, using basically the same experimental paradigm, although with a different baseline, showed a significant activation in the left caudate nucleus for syntactic processing [3]. The use of a different baseline may explain the lack of significant dopaminergic effects in the syntactic condition in the present study. However the baseline task used here appears to be cognitively less demanding (as demonstrated by faster RT) and, in a subtractive logic, we would expect it to unmask additional components in the brain network, rather than masking the network even further. Other factors may explain this somewhat unexpected result, including: i) The effects observed in our previous PET activation study may be ascribed to other neurotransmitter systems. Other neurotransmitters apart from dopamine contribute in cognitive functions [23,24] and possibly also in language processing. ii) A lack of sensitivity in the methodological approach adopted here. The steady-state assumptions made here with respect to dopaminergic modulation may not account for neuromodulatory temporal changes [25].

Conclusion

Our findings provide evidence for a specific involvement of dopaminergic neurons in core grammatical processings in human language.

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Table 1: (^{11}C)Raclopride Binding Potential - Raw Data

Subjects	left VS			left Cau_d			left Put_d		
	Syn	Ph	Bsl	Syn	Ph	Bsl	Syn	Ph	Bsl
subj01	2.89	3.11	3.12	2.58	2.98	3.00	2.37	2.46	2.73
subj02	3.01	3.05	3.13	2.80	2.77	2.77	2.19	2.16	2.22
subj03	3.04	2.94	2.87	3.06	2.74	2.78	2.35	2.22	2.17
subj04	2.91	2.52	2.67	2.54	2.49	2.55	2.10	2.00	1.91
subj05	2.89	2.91	3.23	2.50	2.68	3.03	2.23	2.49	2.48
subj06	3.27	3.30	3.15	2.94	3.24	3.19	2.86	2.45	2.40
subj07	3.35	3.04	3.01	3.07	2.82	2.84	2.15	2.18	2.37
subj08	3.02	2.86	3.20	2.98	3.01	2.89	2.44	2.62	2.50
Mean	3.05	2.97	3.05	2.81	2.84	2.88	2.33	2.32	2.35
St. Dev.	0.17	0.23	0.19	0.24	0.23	0.19	0.24	0.21	0.25

	right VS			right Cau_d			right Put_d		
	Syn	Ph	Bsl	Syn	Ph	Bsl	Syn	Ph	Bsl
subj01	3.05	3.11	2.85	2.33	2.82	2.71	2.47	2.91	2.82
subj02	3.28	3.11	3.31	2.27	2.31	2.44	2.76	2.72	2.70
subj03	3.04	2.91	3.22	2.53	2.32	2.22	2.60	2.43	2.71
subj04	2.90	2.64	2.76	2.19	2.27	2.26	2.45	2.62	2.37
subj05	2.88	3.19	2.99	2.26	2.50	2.48	2.60	2.91	2.84
subj06	3.57	3.69	3.59	2.65	2.69	2.74	2.95	3.05	2.89
subj07	3.28	3.12	3.29	2.53	2.37	2.20	2.93	2.55	2.59
subj08	3.54	3.19	3.28	2.60	2.65	2.37	2.80	2.75	2.81
Mean	3.19	3.12	3.16	2.42	2.49	2.43	2.7	2.74	2.72
St. Dev.	0.27	0.29	0.27	0.18	0.21	0.21	0.19	0.21	0.17

Figure Captions

Figure1: Normalised tracer activity in the cerebellar reference tissue

Frame by frame mean cerebellar activity, normalised to the grand maximum value, for the 3 experimental conditions. Interval bars represent the full range of individual values for each condition. Dashed lines indicate two standard deviations below and above the grand mean cerebellar activity. We found no significant differences of cerebellar activity between conditions (Wilcoxon Signed-Ranked tests, $P < 0.05$).

Figure2: Dopaminergic modulations induced by phonology

Data points and corresponding linear regressions for the two significant correlations between performance and BP values. **A)** The modulation of dopamine release in the left Cau_d specific to Ph compared to Bsl is displayed as a function of the individual differences in Acc in performing Ph compared to Bsl. **B)** The modulation of dopamine release in the left Put_d specific to Ph compared to Syn is displayed as a function of the individual differences in RT in performing Ph compared to Syn.

Figure1

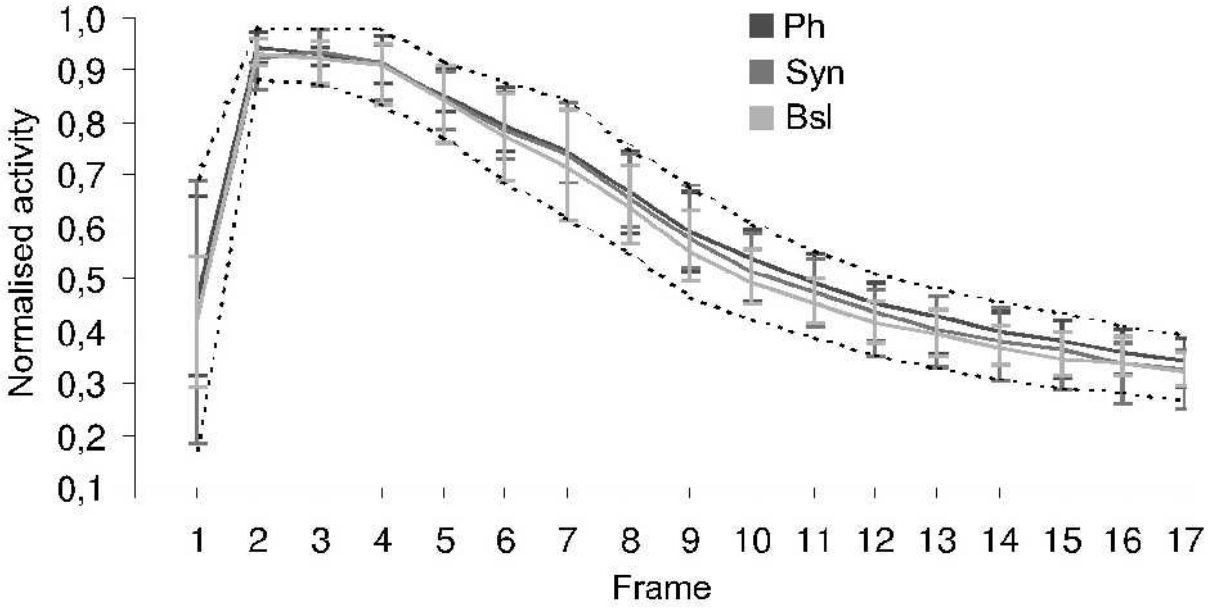
Ph
Syn
Bsl
Normalised activity
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Frame

Figure2