D_2 Antidopaminergic Modulation of Frontal Lobe Function in Healthy Human Subjects

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Background: *Although the major principles of dopamine (DA) signaling have been well described previously, its precise modulatory impact on the prefrontal cortex (PFC) in humans is poorly understood. Two major neurophysiological models propose segregated functional circuits on the systems level as well as D_1 and D_2 receptor-dependent processing states on the cellular level (two-state model).*

Methods: *We examined the predictive validity of these models in 10 healthy male volunteers with a haloperidol challenge (HLP). Cortico-striatal-thalamo-cortical (CSTC) motor loop functions were examined during functional magnetic resonance imaging (fMRI) with a sequential finger opposition task. Neuropsychological implications of the two-state model were evaluated with a test battery of D_1- or D_2-sensitive prefrontal measures.*

Results: *Analysis of fMRI data revealed a significant HLP-induced blood oxygen level dependent–signal decrease in the sensorimotor striatum and a lateralized activation loss of ipsilateral higher order motor cortices and contralateral cerebellum. Neuropsychological evaluation demonstrated a preferential impairment of D_2-sensitive functions, whereas D_1 or non-dopaminergic domains were unaffected.*

Conclusions: *Our data support the hypothesis that mesocortical D_1 and D_2 receptors exert differential influences in the PFC for cognitive function, but the nigrostriatal CSTC network model for the motor domain could not be confirmed.*

Key Words: Dopamine, fMRI, haloperidol, sequential finger opposition, executive functioning

A wide range of behaviors are influenced by the impact of dopamine (DA) on frontal lobe functioning. Although the precise molecular mechanisms are incompletely understood, a particular impact on voluntary motor control and executive functioning has been suggested (for review, see Girault and Greengard 2004). Two different dopaminergic systems have a major impact on prefrontal neural circuits. Mesocortical DA projections play a decisive role in the modulation of D_1 receptor occupancy levels (Goldman-Rakic et al 2000; Mattay et al 2003) and associated cognitive functions, especially working memory (Fuster 1990; Goldman-Rakic 1995; Meyer-Lindenberg et al 2005b). According to the two-state model of Seamans et al (2001), activation of mesocortical D_1 receptors has a tendency to stabilize a single cognitive representation over time, whereas D_2 receptor action facilitates the formation of and switching between multiple network representations (Durstewitz et al 2000a, 2000b; Seamans et al 2001).

Nigrostriatal DA neurons exert their influence on the prefrontal cortex (PFC) via modulation of several feedback loops. According to Alexander's cortico-striatal-thalamo-cortical (CSTC) network model (Alexander et al 1986, 1990), at least four functionally segregated circuits can be distinguished (sensorimotor, oculomotor, cognitive, limbic) that shape the excitatory input provided by thalamo-cortical efferents (Nakano et al 2000; Smith et al 1998). By employing simple motor activation paradigms, several research groups have examined the predictive validity of the CSTC network model in various "DA dysbalanced" states (e.g., in Parkinson's disease [PD] patients with a reduced DA production and turnover) (Brooks 2001; Goerendt et al 2003; Sabatini et al 2000). Most studies have provided evidence for a primary somatomotor (SMC) and a supplementary motor area (SMA) hypoactivation in PD that was responsive to treatment with a DA agonist, in line with the CSTC concept of a "functional deafferentation" of the frontal cortex from excitatory thalamic outflow (Buhmann et al 2003; Jenkins et al 1992; Rascol et al 1992; Samuel et al 2001). Other research findings cast doubt on the capacity of the CSTC network model to explain functional effects (e.g., activation increases of primary and premotor cortices [PMCs] that have been occasionally observed in PD) (Haslinger et al 2001; Sabatini et al 2000; Samuel et al 1997). Current empirical knowledge of motor loop dysfunctions thus remains limited. This is attributable partly to a lack of appropriate experimental designs with the capacity to disentangle primary motor pathology from the confounding effects of task performance, dopaminergic medication, and compensatory cortical reorganization.

The separation of these confounding variables is a major goal of the current research. The present study is to our knowledge the first performance-controlled imaging study that examines the predictive validity of the CSTC network model with haloperidol-induced alterations of motor loop functioning in healthy volunteers. On the basis of previous findings (Bartlett et al 1994; Buchsbaum et al 1999; Miller et al 1997; Tamminga and Holcomb 2001), we expected a striatal activation increase and frontocortical activation decrease after selective D_2 dopaminergic blockade (Figure 1). Furthermore, no previous challenge study has developed neuropsychological hypotheses from empirical theories that assume a receptor-dependent dopaminergic modulation of PFC functions. On the basis of the two-state model (Seamans et al 2001), we predicted a task-dependent vulnerability of different prefrontal cognitive domains to D_2 antidopaminergic challenge. More precisely, at the behavioral level, we predicted preferential impairment of executive tasks with a high emphasis on cognitive-behavioral integration and response flexibility (possibly

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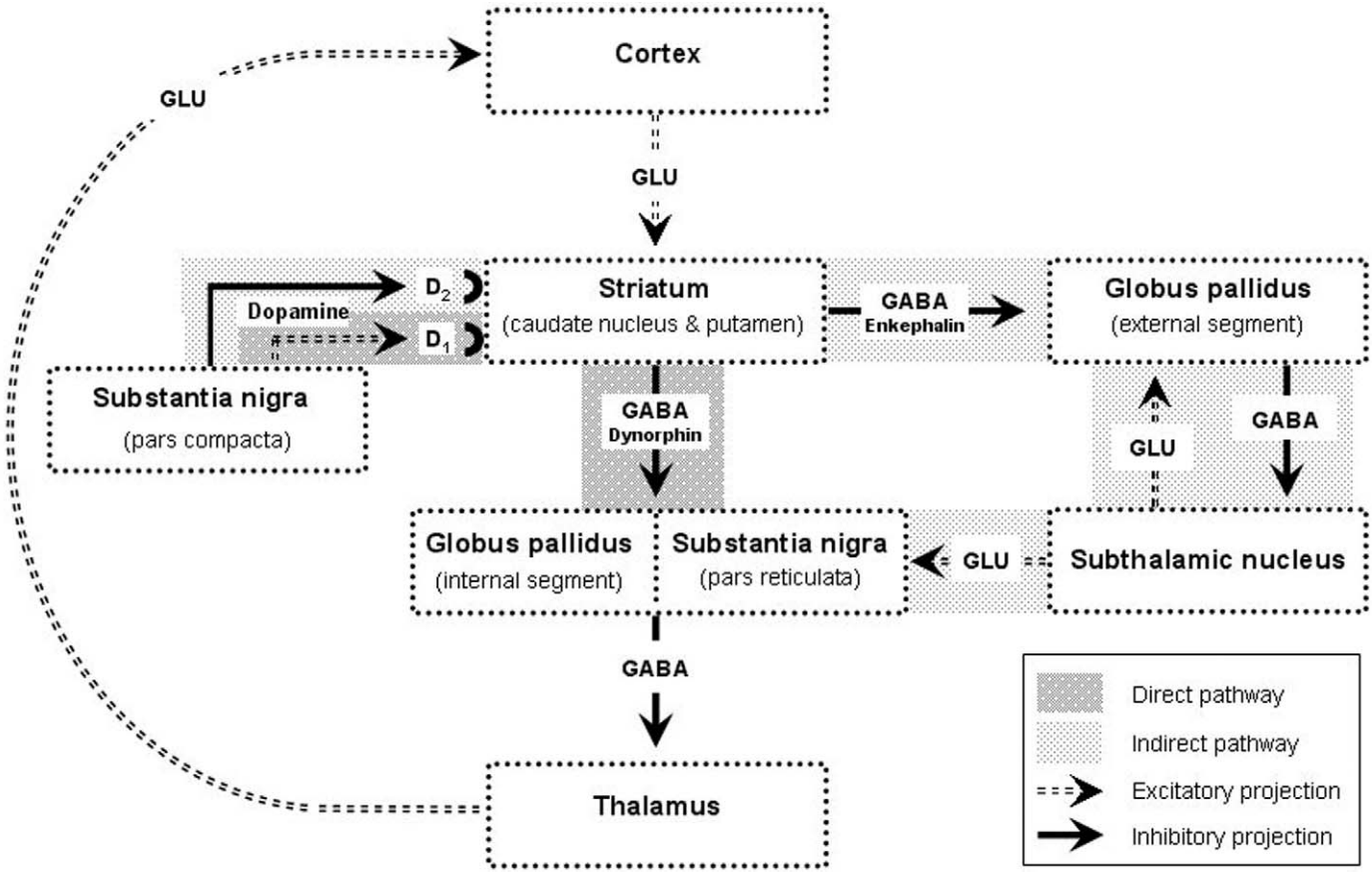

Figure 1. Schematic illustration of the cortico-striatal-thalamo-cortical (CSTC) circuitry (Alexander et al 1986). The tonic inhibitory influence of the output module on thalamo-cortical efferents is modulated by the direct (D_1-dynorphin) and indirect (D_2-enkephalin) processing pathway of the basal ganglia. In the scenario of a haloperidol challenge, a striatal activation increase and frontocortical activation decrease is predicted (blockade of striatal D_2-receptors → reduced action of local inhibitory G-proteins → activation increase of the input module of the indirect pathway → overbalancing of the direct pathway → increased γ-aminobutyric acid [GABA]ergic action of internal pallidal and nigral efferents on the thalamus → PFC depression). GLU, glutamic acid.

D_2-dominated, e.g., attentional set shifting, response inhibition, cognitive interference) and a relative sparing of tasks focusing on the active mnemonic "holding" of items (possibly D_1-dominated, e.g., working memory).

Methods and Materials

Subjects

We investigated the influence of a single dose of haloperidol on cognitive performance and motor activations in 10 healthy men (naive to neuroleptics; mean age: 23.4 ± 1.7 years). The volunteers had no history of significant general medical, neurological, or psychiatric disorders. Written informed consent was obtained after a full explanation of the purpose and procedures of the study had been given. With a prospective approach, neuropsychological and functional magnetic resonance imaging (fMRI) procedures were performed three times: before substance dosing (t_1 = neuroleptic-naive), 1 hour after haloperidol challenge (HLP) infusion of 5 mg/70 kg (t_2), and again 24 hours later, after approximately one half-life interval of the neuroleptic agent (t_3) (Magliozzi and Hollister 1985). Data collection was conducted under single-blind conditions with physiological saline administered by intravenous drip infusion at the first and third acquisition date. Data acquisition was performed within a time frame of 60–150 min after infusion. Sequencing of cognitive tests as well as the order of the fMRI and neuropsychological acquisition blocks were varied in a pseudo-randomized manner. The imaging data of two participants were excluded from fMRI analysis at a later date: one on the grounds of left-handedness, and the other because of severe motion artifacts. The remaining eight participants of the fMRI experiment were dominant right-handers (lateralization quotients [LQ] > 50), as determined by the Edinburgh Handedness Inventory (EHI) (Oldfield 1971). The study was approved by the local university ethics committee.

Neuropsychological Assessment

Neuropsychological evaluation included assessment of several cognitive domains associated with the integrity of the frontal lobes. Data acquisition focused on those cognitive abilities known to be critically influenced by mesocortical and nigrostriatal projections and, hence, alterations of DA signaling. Basic parameters of voluntary motor control (e.g., motor speed) were determined with the computerized Test Battery for Attentional Performance (TAP, Zimmermann and Fimm 1994). Abstract reasoning was evaluated by use of the Wisconsin Card Sorting Test (WCST, Heaton 1993). Selective attention was examined with a Continuous Performance Test (CPT), employing a dense presentation of target, non-target, and distractor stimuli for the persistent challenge of attentional and behavioral set-shifting. Susceptibility to cognitive interference was examined with the TAP-incompatibility task, with incongruent stimulus and response attributes to elicit global action tendencies during choice

reactions. Integrity of the working memory domain was investigated with a classical 2-back task (TAP), asking participants to memorize an ongoing set of letter presentations and indicate whenever a current item matches the last but one. A further measure was employed as "non-dopaminergic control task," assessing a phenomenon not primarily attributable to the prefrontal lobe: the extent of motor acceleration in response to an audio warning tone (TAP phasic alertness). This function is mediated by transient arousal enhancements arising from noradrenergic projections of the brainstem ascending reticular activating system.

With the exception of the WCST, all instruments were reapplied in a pseudo-randomized manner at the second and third appointment date, respectively. During the evaluation of performance data, special care was taken to rule out potential error inflation secondary to subtle extrapyramidal side effects (EPS; e.g., as indicated by target omissions followed by inadequate reactions with a non-physiologically low reaction time). Statistical analyses were conducted with a standard software package (SPSS 10.0, Chicago, Illinois). Significant performance differences between acquisition dates were determined with one-way analysis of variance (ANOVA) for repeated measurements. For post hoc comparison, one-tailed Wilcoxon tests for paired samples were performed, and all results were subsequently corrected for multiple comparisons.

fMRI Paradigm

The motor activation paradigm consisted of a self-paced, unrestrained sequential finger opposition (SFO) task with enhanced flexibility and response inhibition demands. Task performance required continuous thumb-to-finger coordination according to the scheme II-III-IV-V-IV-III-etc. (II = index, III = middle, IV = ring, V = little finger), thus involving the recurrent inhibition of the ongoing motor sequence followed by a subsequent change in tapping direction. For a further augmentation of neural processing demand, the non-dominant left hand was used. Before the fMRI experiment, all subjects performed the task outside of the magnet with no apparent difficulties. To reduce motion artifacts, a sub-maximal performance rate of 2 Hz was rehearsed. Subjects were instructed to maintain the rehearsed tapping rate, amplitude, and thumb-to-finger pressure as constantly as possible over the various imaging sessions. Inside the magnet, the paradigm was performed in a block-design fashion with resting periods of 40 sec alternating with 40 sec of motor activation (five intervals per condition). All participants kept their eyes closed during fMRI procedures and used headphones to minimize scanner noise. Head fixation was improved by a vacuum pad placed inside the head coil. The start of each rest/activation cycle was initiated by a verbal command, and finger tapping performance was visually monitored and recorded by an on-site observer. The SFO task performance parameters were defined as the average number of finger oppositions (tapping amount) and sequencing faults (tapping accuracy) per activation cycle of 40 sec, respectively.

Imaging Procedure

Magnetic resonance imaging was performed on a clinical 1.5 T whole body scanner (Siemens Vision, Erlangen Germany) equipped with a standard circularly polarized (CP) head coil. For functional imaging, a echo-planar imaging sequence (repetition time = 4000 msec, echo time = 60 msec, $\alpha = 90°$) with an inplane resolution of 3.43 mm × 3.43 mm (28 slices, 4 mm thickness, 1 mm gap, 220 mm field of view) was used. Slices were orientated axially parallel to the anterior commisure and posterior commisure plane as defined by (Talairach and Tournoux 1988). Each functional T2* slice was imaged 100 times in a total period of 400 sec.

fMRI Data Processing and Statistical Analysis

Image processing and statistical analyses were carried out with the software package SPM2 (Wellcome Institute of Cognitive Neuroscience, London, United Kingdom). For statistical analysis, the alternating activation and resting periods were modeled in a general linear model with a box-car reference vector convolved with a hemodynamic response function to account for the delay and dispersion of the blood oxygen level dependent (BOLD) response. The resulting statistical parametric map constituted a t-statistic for each voxel in every subject. For whole group statistics, the contrast images of all subjects were included into a second-level analysis with a threshold criterion of $T \geq 3.5$ for 15 or more contiguous voxels. Regional effects were accepted as significant if the p value for the cluster size (cerebral and cerebellar cortex) or the volume of the circumscribed anatomical area (subcortical nuclei) exceeded a size corresponding to a threshold of at least .05 corrected for multiple comparisons. One-sample t-tests were performed to test for in-group correspondences at imaging sessions. T-tests for paired samples were conducted to assess significant functional alterations associated with the immediate impact of haloperidol ($t_1 > t_2$, $t_1 < t_2$). Over all three acquisition dates, one-way ANOVA was performed to identify activity changes that matched HLP pharmacokinetics. Linear contrasts were defined according to the assumption of an initial substance-induced BOLD–suppression (or –augmentation), followed by a partial functional restoration (or decline) at plasma elimination half-life (i.e., $t_1 >> t_2 < t_3, t_1 << t_2 > t_3$).

Functional lateralization of motor cortices was examined with a region-of-interest (ROI) approach with masks created with the WFU PickAtlas utility (Maldjian et al 2003). Anatomical ROIs were defined according to Brodmann areas (BAs), with BA 04 corresponding to the primary motor cortex, and BA 06 corresponding to the SMA and PMC, respectively. Weighted ROI LQs were determined according to the method specified in detail by Fernandez et al (2001) and Bertolino et al (2004) with individual thresholds for each subject. An individual threshold t_I was defined as 50% of the mean of the 5% highest t values in the individual SPM-t-map.

Lateralization quotients were calculated following the formula:

$$LQ = \frac{\sum_{v \in V_R,\ t_v \geq t_I} t_v \ - \ \sum_{v \in V_L,\ t_v \geq t_I} t_v}{\sum_{v \in V_R,\ t_v \geq t_I} t_v \ + \ \sum_{v \in V_L,\ t_v \geq t_I} t_v}$$

where V_R and V_L are the sets of all voxels in the particular ROI, right and left respectively, and t_v is the t value in voxel v.

Results

Behavioral Observations and SFO Performance

Seven of the 10 volunteers experienced mild subjective symptoms of akathisia after venous infusion that abated within 24 hours. No overt extrapyramidal side effects such as dyskinesia, dystonia, or Parkinsonism were observable at any time. Although the participants were blind to the experimental design, motor coordination, timing of SFO movements, and attentional performance were reported as being substantially more demanding at the second acquisition date. Two of the 10 subjects felt

Table 1. Behavioral Performance Parameters

	t_1	t_2	t_3	ANOVA	Post Hoc Comparison (t_1-t_2/t_2-t_3)[a]
SFO Task Performance					
SFO rate (Hz)	2.4 ± 1.2	2.3 ± 1.3	2.3 ± .8	ns	—
Tapping accuracy (sequencing errors)	14.9 ± 5.5	20.8 ± 6.7	20.1 ± 11.2	ns	—
Cognitive Capabilities					
Motor speed (ms)	185 ± 20	203 ± 23	189 ± 19	$p < .0001$, [$F(2,18) = 17.0$]	$t1 < t2$: $p < .005$ ($z = -2.8$) $t2 > t3$: $p < .007$ ($z = -2.7$)
Attentional set shifting (errors)	4.0 ± 2.0	8.0 ± 4.4	3.6 ± 2.7	$p < .038$, [$F(1.1,8.0) = 6.0$[b]]	$t1 < t2$: $p < .042$ ($z = -2.0$) $t2 > t3$: $p < .092$ ($z = -1.7$)[c]
Cognitive Interference (errors)	4.8 ± 2.7	5.9 ± 3.6	6.9 ± 3.0	$p < .023$, [$F(2,18) = 4.7$]	$t1 < t2$: $p < .047$ ($z = -2.0$) $t2 > t3$: ns
Working memory (errors)	2.0 ± 2.0	1.9 ± 2.2	1.3 ± 1.6	ns	—
Phasic alertness (ms acceleration)	2.0 ± 5.5	9.5 ± 14.1	6.9 ± 10.2	ns	—

Mean ± standard deviation. ANOVA, analysis of variance; SFO, sequential finger opposition.
[a]Wilcoxon test for paired samples, one-tailed, corrected for multiple comparisons.
[b]Greenhouse-Geisser adjusted.
[c]Marginally significant ($.05 < p < .10$).

unable to complete the CPT task at time t_2 (but not at t_1 or t_3), and the test had to be discontinued at their request. One-way ANOVA revealed no significant differences in the amount of tapping [$F(2) = .12$, $p < .89$] or tapping accuracy [$F(2) = 1.81$, $p < .20$] between measurements dates. Although the mean tapping rate remained virtually constant, a descriptive tendency toward a decline in precision after venous administration was observed (see Table 1 and Figure 2).

Main Effects of Task

Main functional effects of SFO task execution were determined from the fMRI data obtained during the neuroleptic-naive state (t_1), demonstrating finger tapping performance to be associated with a significant activation enhancement of a highly distributed motor network (see Table 2, Figures 3 and 4). Major activations were found in the ipsilateral cerebellum (dentate nucleus and lobule HVI according to Larsell's roman numeral

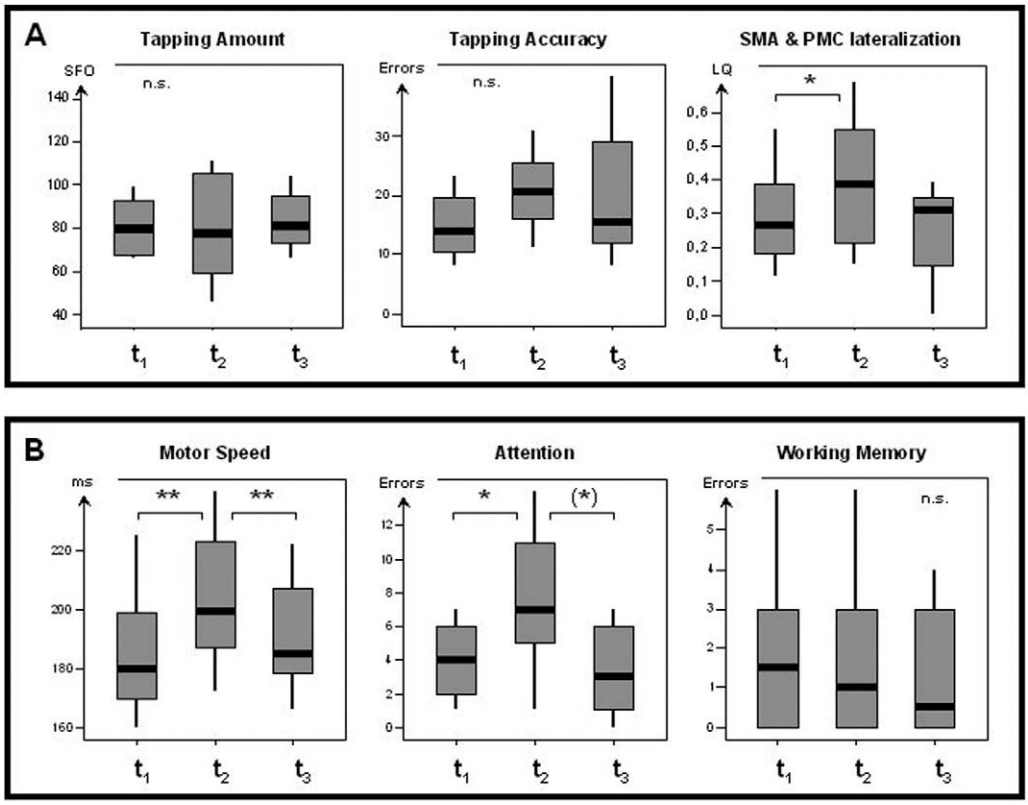

Figure 2. Boxplot illustration of (A) functional magnetic resonance imaging (fMRI) sequential finger opposition (SFO) motor task and (B) neuropsychological test performance variations between acquisition dates: t_1 = neuroleptic-naive, t_2 = acutely haloperidol challenge (HLP) medicated, $t3$ = at HLP half life (see Table 1 and text for further details). SMA, supplementary motor area; PMC, premotor cortex; LQ, lateralization quotient.

Table 2. Main Effect of SFO Task Performance (t_1)

			Talairach Coordinates[a]					
	Hemisphere	Brodmann Area[a]	*x*	*y*	*z*	Cluster Size	T-Value[a]	*p*-Value[b]
SMC, dPMC	right	1–4, 6	35	−15	45	1340	18.8	$p < .0001$
SMA[c]-dACG	right & left	6, 8, 24, 32	6	0	48	1340	14.3	$p < .0001$
	left	4, 6	−24	−1	39	212	12.3	$p < .0001$
SMC-dPMC[d]	left	4, 6	−39	0	53	212	9.0	$p < .0001$
	left	4, 6	−56	2	39	212	8.0	$p < .0001$
vPMC[d]–Insula	right	44, 13	62	12	13	47	8.1	$p < .0001$
	left	44, 13	−50	6	3	24	6.2	$p < .0330$
Lentiform nucleus[e]	right	–	27	0	−8	72	7.0	$p < .0001$
	left	–	−24	0	−5	28	5.6	$p < .0001$
Thalamus	right	–	15	−20	4	220	11.3	$p < .0001$
	left	–	−12	−20	1	34	7.6	$p < .0001$
Cerebellum	right	–	27	−56	−20	1337	35.3	$p < .0001$
	left	–	−18	−60	−37	1337	35.3	$p < .0001$

SMC, somatomotor cortex; dPMC, dorsal premotor cortex; SMA, supplementary motor area; dACG, dorsal anterior cingulate gyrus; vPMC, ventral premotor cortex.

[a]Local maximum.

[b]All *p* values are corrected for multiple comparisons for the cluster size (cerebral and cerebellar cortex) or the volume of the anatomical area (subcortical nuclei).

[c]Includes two functionally dissociable subareas: pre-SMA (rostral) and SMA proper (caudal), separated by convention through a vertical line that intersects the anterior commissure (for a comprehensive discussion, see Riecker et al 2003).

[d]Fits the known location of the dorsal and ventral forelimb representations of the PMC, respectively (Haslinger et al 2002; Takada et al 1998).

[e]Putamen and internal/external globus pallidus.

nomenclature; see Larsell and Jansen 1972) and contralateral cerebral cortex, especially the contralateral somatomotor cortex (extending to the posterior-parietal cortex), dorsal premotor cortex (dPMC), and the mesial SMA (including SMA proper, pre-SMA, and dorsal parts of the anterior cingulate gyrus [ACG]). Weaker activations were associated with the contralateral lentiform nucleus, thalamus, insula, and the adjacent ventral premotor cortex (vPMC). Despite the clear lateralization of task-related activations, substantial recruitment of respective motor areas of the opposite hemisphere was evident throughout the network (see Table 2 for detailed anatomical specifications).

Antidopaminergic Interaction Effects

A subset of the imaged motor areas exhibited a significant BOLD diminishment after venous administration (see Table 3, Figures 3 and 4). Main functional decreases included a large mesial cluster covering pre-SMA, SMA proper, and dorsal ACG (located around the border of BA 24 and BA 32). Further significant reductions in activation affected the ipsilateral SMC, ipsilateral dPMC, and contralateral cerebellum as well as the ipsilateral putamen, the adjacent ipsilateral vPMC, and the right posterior parietal cortex. In general, the HLP-induced activation loss seemed to be lateralized, involving preferentially the motor

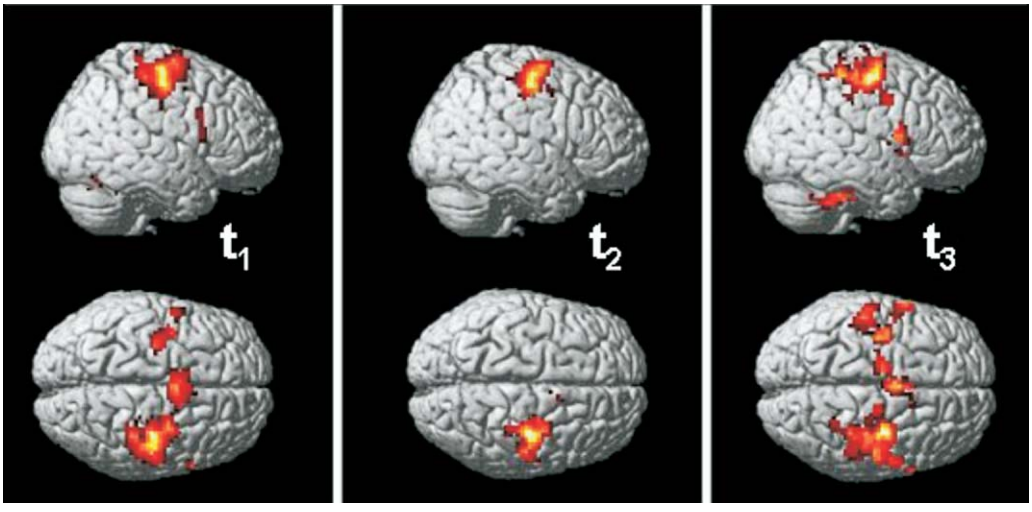

Figure 3. Descriptive comparison of sequential finger opposition (SFO) motor network activation differences between acquisition dates: t_1 = neuroleptic-naive, t_2 = acutely haloperidol challenge (HLP) medicated, t_3 = at HLP half life (one-sample *t*-tests, $p < .001$ uncorrected).

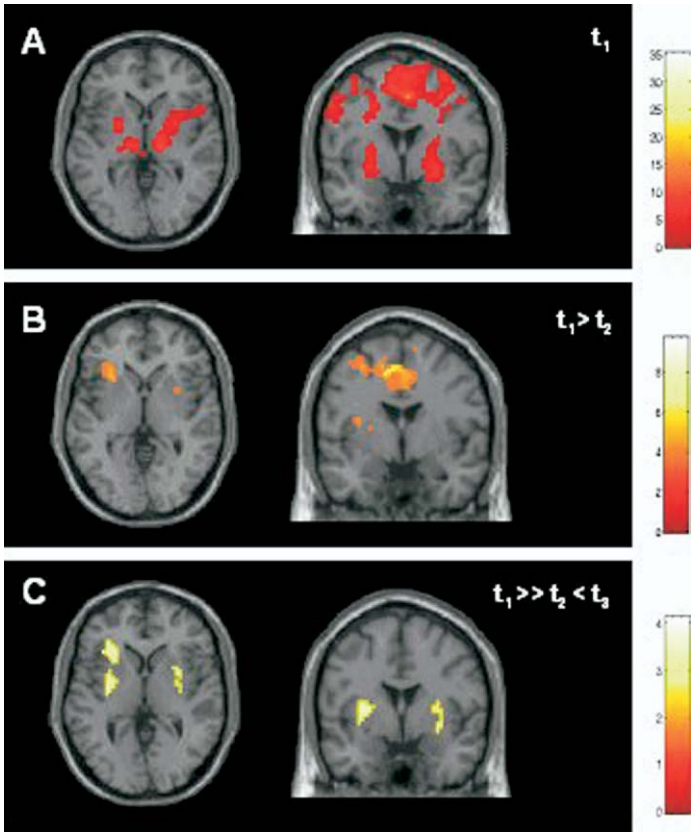

Figure 4. Statistical parametric maps of motor network constituents ($z = 11$, $y = -4$): (A) significant activations during sequential finger opposition (SFO) performance in the neuroleptic-naive state (one-sample *t*-tests $p < .001$, uncorrected), (B) subset of regions exhibiting an immediate blood oxygen level dependent (BOLD)-suppression after haloperidol challenge (HLP) application (paired *t*-test, $p < .005$ uncorrected), (C) putaminal activity level approximates HLP availability course (analysis of variance $p < .005$ uncorrected; see Tables 2 and 3 for further details).

Table 3. Antidopaminergic Interaction Effects

	Hemisphere	Brodmann Area[a]	Talairach Coordinates[a]			Cluster Size	T-Value[a]	*p* Value[b]
			x	*y*	*z*			
Paired *t*-test: $t_1 > t_2$[c]								
SMC-dPMC	left	4, 6	−33	−18	42	62	5.2	$p < .014$
SMA proper-dACG	right and left	6, 8, 24, 32	−12	−4	44	365	9.8	$p < .0001$
Pre-SMA	right and left	6, 8, 24, 32	9	15	42	365	9.8	$p < .0001$
	right and left	6, 8, 24, 32	−6	17	41	365	9.8	$p < .0001$
vPMC–Insula	left	44, 13	−33	27	10	106	5.1	$p < .0001$
Putamen	right	–	33	6	0	21	3.8	$p < .018$
	left	–	−30	−11	11	43	4.8	$p < .003$
PPC	right	5	−24	−41	59	110	8.2	$p < .0001$
Cerebellum	right	–	27	−53	−20	88	6.6	$p < .001$
	right	–	21	−54	−33	64	5.9	$p < .012$
ANOVA: $t_1 >> t_2 < t_3$[d]								
Putamen	right	–	33	−3	−5	16	3.1	$p < .063$
	left	–	−30	3	8	74	4.1	$p < .005$

SMC, somatomotor cortex; dPMC, dorsal premotor cortex; SMA, supplementary motor area; dACG, dorsal anterior cingulate gyrus; vPMC, ventral premotor cortex.

[a]Local maximum.

[b]All *p* values are corrected for multiple comparisons for the cluster size (cerebral and cerebellar cortex) or the volume of the anatomical area (subcortical nuclei).

[c]Paired *t*-tests $t_1 < t_2$ and $t_2 < t_3$: no significances.

[d]Analysis of variance (ANOVA) $t_1 << t_2 > t_3$: no significances.

network areas of the non-dominant hemisphere, in relation to task side (ipsilateral: first- and second-order motor cortices, thalamus, putamen; contralateral: cerebellum). The indicated lateralization enhancement of motor cortices at t_2 was confirmed by the statistical comparison of calculated LQs, yielding a significant LQ increase for the higher order motor cortices (premotor and supplementary motor cortex, Wilcoxon $z = -2.10$; $p < .018$) and a corresponding data trend for the primary motor cortex (Wilcoxon $z = -1.54$; $p < .061$). Over all test dates, only the functional time course of the putamen significantly matched the pharmacokinetic profile of haloperidol ($t_1 >> t_2 < t_3$). This drug effect was again especially pronounced in the ipsilateral hemisphere, expanding from the putamen to the adjacent areas of the vPMC (see Figure 4).

Neuropsychological Performance

Analysis of WCST data confirmed normal problem-solving capacity with no cognitive flexibility restraints for all subjects at baseline (all performance parameters above the 50th percentile rank). With respect to D_2-antidopaminergic challenge, one-way ANOVA revealed a certain vulnerability profile over the different neuropsychological test domains (see Table 1 and Figure 2). Significant changes in motor speed [$F(2) = 17.03$, $p < .0001$] followed the course of the assumed drug efficacy, with a significant reduction in the acutely medicated state (Wilcoxon $z = -2.8$; $p < .005$) followed by a corresponding restoration at half-life degradation (Wilcoxon $z = -2.7$; $p < .007$). Attentional set shifting [$F(1.1) = 5.95$, $p < .038$] and cognitive interference capabilities [$F(2) = 4.67$, $p < 023$] were likewise affected by HLP infusion. With an acute deterioration at t_2 (Wilcoxon $z = -2.0$; $p < .042$) and a clear normalization trend at half-life (Wilcoxon $z = -1.7$; $p < .092$), alterations of attentional capabilities likewise matched the pharmacokinetic profile of haloperidol.

Contrary to this, basic working memory capabilities were not significantly affected by D_2-blockade [$F(2) = 2.07$, $p < .16$]; the descriptive data trend suggests a rehearsal-induced improvement of working memory performance over measurement dates rather than a deterioration (see Table 1). Similarly, the performance on the phasic alertness task was not significantly affected by D_2-blockade [$F(2) = 1.81$, $p < .19$] The descriptive data trend suggests a t_2 motor acceleration gain rather than a loss, indicating the partial overriding of HLP-induced motor constraints by the transient arousal inductions (see Table 1).

Discussion

Functional Correlates of SFO Task Performance

As expected, execution of the SFO task induced a significant activation enhancement over all submodules of the CSTC motor network. Main fMRI task effects were focused on the contralateral "hand knob" area of the SMC and ipsilateral cerebellar regions that correspond to the input (lobule HVI) and output (dentate nucleus) nodes of PFC motor information (Desmond et al 1997; Larsell and Jansen 1972; Yousry et al 1997). The spatial location of subcortical activations is similarly conclusive, because they match the forelimb representation of the sensorimotor striatum (Scholz et al 2000) and the main origin (ventral posterior/ventral lateral nucleus) of thalamic efferents feeding the PMC and SMC (Schell and Strick 1984; Takada et al 1998).

Compared with the activity patterns elicited by simple tapping tasks (e.g., Rao et al 1996; Riecker et al 2003; Solodkin et al 2001), the SFO network demonstrates the recruitment of brain areas concerned with more complex behavioral processing. The concurrent activation of the dorsal and ventral PMC hand motor areas, for instance, is consistent with the execution of a sophisticated task structure involving multiple effectors and sequence transitions (Harrington et al 2000; Mushiake et al 1991; Takada et al 1998). The pronounced involvement of the mesial PFC suggests the processing of higher motor selection demands (Barch et al 2000), organization of the temporal structure of multiple movements (Tanji 2001), and inhibition of inadequate responses (Mostofsky et al 2003; Rubia et al 2001). Further empirical evidence for pronounced executive processing demands comes from the poor lateralization of our initial SFO motor network. As has been frequently observed by other research groups, the pronounced recruitment of ipsilateral cortical and contralateral cerebellar submodules indicates substantial task load increases during unilateral exercise (e.g., the execution of a complex task structure) (Catalan et al 1998; Haslinger et al 2002; Mattay et al 1998; Scholz et al 2000), lack of familiarity with the task, or use of the non-dominant hand (Kawashima et al 1993; Solodkin et al 2001). This "lateralization loss" is typical for the higher order motor areas (especially SMA and PMC) and has been interpreted as an indication of their fundamentally different (i.e., higher executive) roles in motor control (Solodkin et al 2001).

Haloperidol Challenge of Motor Loop Functioning

Our data suggest that the CSTC network model is only partially successful in predicting haloperidol-induced alterations in motor functioning. The t_2 activation decrease of PMCs is fairly compatible with the concept of a transient "functional deafferentation" of the PFC from excitatory thalamic outflow (Kievit and Kuypers 1977; Middleton and Strick 2000). The subcortical outcome of DA challenge, however, clearly contradicts the predictions of the model. Although we observed an immediate drug effect on the sensorimotor striatum ($t_1 > t_2$) that significantly matched our rough linear approximation of the bioavailability course ($t_1 >> t_2 < t_3$), the functional alteration was found to be a putaminal activation decrease rather than the expected activation increase.

The basal ganglia (BG) finding is at first sight surprising, because haloperidol-induced increases in striatal metabolic rates have been repeatedly reported in earlier resting state studies (Buchsbaum et al 1992, 1999; Miller et al 1997; Tamminga and Holcomb 2001) and explained within the proposed functional microcircuitry of the BG (see Figure 1). On closer inspection, however, our finding adds to accumulating evidence against static and overly simplistic BG models, at least in the prediction of the functional dynamics of the "actively behaving" brain (Aizman et al 2000; Floresco et al 2003; Obeso et al 2000; Seiss and Praamstra 2004; Waszczak et al 2002). Current concepts of DA functioning account for the modulation of the task-related to task-unrelated neural activity as an essential feature of the dopaminergic "tuning" of neural networks (Grace 1993; Meyer-Lindenberg et al 2005a; Seamans and Yang 2004; Williams and Goldman-Rakic 1995). As compared with the resting state results, our BG finding might thus simply reflect a different (i.e., task- and not resting-related) tuning state of striatal processing. This assumption is supported by the likewise CSTC-model incongruent observation of a striatal metabolism decrease during abstract planning that was demonstrated in a recent sulpiride challenge study (Mehta et al 2003). Descending PFC glutamatergic fibers that synapse in proximity to the axon terminals of DA neurons might be involved in this process (Morari et al 1998; Nakano et al 2000; Strafella et al 2001).

At the cortical level, the striking lateralization of the HLP-induced activation loss warrants further discussion. As already

shown, significant antidopaminergic effects were largely restricted to higher order processing modules known to be involved in executive motor control, selective attention, and working memory (e.g., ipsilateral PMC and SMA, posterior parietal cortex, contralateral cerebellum). In contrast, the neurophysiological response of the basic output modules (contralateral SMC, ipsilateral cerebellum) proved insensitive to DA challenge. The precise neurophysiological background of this functional dissociation is, however, currently unknown. The observed hypoactivations are below the threshold for overt behavioral changes (i.e., they can not be explained simply by a drug-induced alteration of task performance).

Taken together, our findings point to a preferential vulnerability of higher executive modules of the motor system to antidopaminergic changes, an outcome that fits in well with current empirical models of mesocortical functioning. Mesocortical DA is thought to modulate the signal-to-noise ratio of PFC networks according to an inverted-U–shaped dose-response curve (Meyer-Lindenberg et al 2005a; Williams and Goldman-Rakic 1995; Winterer and Weinberger 2004). Variables that drive the baseline DA level away from its "optimal tone" encourage the physiological and behavioral breakdown of PFC functions, a fact that has been convincingly established in the cases of pharmacological challenge (Mattay et al 2000), PFC capacity overload (Callicott et al 1999), and genetic variants of DA-degrading enzymes (Egan et al 2001; Mattay et al 2003; Meyer-Lindenberg et al 2005a). Because our unilateral SFO task involved the employment of higher executive function (e.g., on-line representation of task sequence), the haloperidol-induced BOLD-attenuation might resemble a behaviorally compensated state of suboptimal DA signaling in the (lateralized) executive components of the motor system. Such effects could be mediated by indirect effects of D_2 blockade on D_1 receptor availability or be related to direct effects of D_2 receptor antagonists on bursting behavior of PFC neurons (Wang et al 2004). The notion of an HLP-induced "leftward shift" on the inverted-U curve is supported by the behavioral data, indicating an impending capacity overload of higher order motor control functions (e.g., sequencing error increment, reported performance-related attentional exhaustion).

In addition to small sample size and lack of determination of serum drug level, some other limitations of our study warrant further consideration. Firstly, the observed antidopaminergic changes might be confounded with non-specific time and order effects due to the sequential nature of our experimental design. Secondly, although haloperidol possesses a high specificity for postsynaptic D_2 receptors, a small action on D_1 dopaminergic, $5HT_2$ serotonergic, and α_1 adrenergic receptors has been described (Closse et al 1984). We thus cannot fully exclude that our results are partly influenced by the concurrent challenge of other neurotransmitter systems. Thirdly, although our laterality analysis is a well-established approach that accounts for the between-subject variability of activation levels, the evidenced effects are potentially biased by threshold effects, because statistical comparisons are performed on the basis of provisional individual statistics.

On a more general level, our conclusions are limited by the restricted specificity and sensitivity of the BOLD contrast to neuronal activation. Because dopaminergic agonists and antagonists can act as vasoconstrictors and vasodilators on DA receptors embedded in cerebral artery walls (Edvinsson et al 1978), the observed antidopaminergic effects might be confounded with uncoupling phenomena of the neurovascular response (i.e., the vascular signal measured with fMRI is no longer a reliable indicator of changes in neuronal activity; see also Callicott et al 1999). This is, however, unlikely to occur within circumscribed brain regions. Moreover, pathophysiological inferences on motor functioning in Parkinson's disease are limited by the fact that not all effects of long-term DA depletion are easily reflected by alterations of the BOLD-response after transient D_2 depolarization blockade. Further empirical studies are necessary to corroborate the proposed DA dose- and load-dependence of higher executive motor processing, related shifts of functional lateralization, and possible implications for the neuropsychiatric field (e.g., lateralization disturbances in schizophrenia).

D_2-Antidopaminergic Modulation of Higher Cognitive Functions

Two cognitive key domains of the PFC resemble opposite poles of the same functional continuum: the ability to preserve and use mental representations over delay periods, and to flexibly shift between different cognitive and behavioral sets. The preferential modulation of the mnemonically "adhering" dimension by mesocortical D_1 receptors is a well-established finding of PFC research (Floresco and Phillips 2001; Williams and Goldman-Rakic 1995). On the basis of previous neurophysiological data, we hypothesized a D_2-antidopaminergic susceptibility of the opposing "flexible" pole. As predicted by our working hypothesis, an immediate deterioration of PFC functions was observed after haloperidol administration, with a particular effect on tasks with a high load on attentional set shifting, response flexibility, and timing (selective attention, cognitive interference, motor speed). Consistent with subliminal EPS, a concurrent disturbance of response initiation was observed. This did not, however, likely account for the enhanced error rates of the cognitive domains, because a potential error inflation due to EPS-induced omissions or commissions was ruled out by our data analysis. Again, as predicted by our hypothesis, D_1-dopaminergic and noradrenergic functions remained unaffected (working memory, phasic alertness), a fact that is highly suggestive of the separation performance of the proposed D_2-dopaminergic profile.

Beyond the behavioral level, our findings corroborate the main physiological tenets of Seamans and Durstewitz's (2001) two-state model of PFC functioning (Durstewitz et al 2000a, 2000b; Seamans et al 2001). The authors predict the formation of sustained and noise-resistant neural activity states from extrasynaptic (i.e., tonic) D_1-receptor stimulation, a neural condition, that seems to "lock working memory buffers into a single mode of action, such that one or a few representations completely guide action at the expense of response flexibility" (Seamans and Yang 2004). Under physiological circumstances, the described dynamic is thought to be regularly reset by high levels of intrasynaptic (i.e., phasic) DA, a setting that promotes the establishment of transient D_2-dominated network states with a net reduction in inhibition. The resulting increment of low-gain network representations seems to facilitate the handling of more "flexible" cognitive demands (e.g., allows the integration of multiple behavioral options). Under the D_2-antidopaminergic influence of HLP, an unphysiological bias toward the D_1-dependent "adhering" network state is predicted, with the accordant D_2-dependent deficits evidenced in our study.

The notion of a connection of D2-receptor action and the "flexible" pole of PFC functioning is supported by recent empirical evidence (e.g., studies in rodents [Floresco et al 2006; Goto and Grace 2005] and healthy volunteers [Mehta et al 2004] that indicate a critical role of D2 receptor functioning in attentional set shifting). A recent work by Wang et al (2004) expands on this view by indicating a functional specificity of DA receptor subtypes to different intercepts of the "perception-action cycle"

(Fuster 1990) of cognitive tasks. Although the mnemonic-related discharge of dorsolateral PFC pyramidal cells proved to be sensitive to D_1 receptor challenge, neural firing associated with the cognitive-behavioral integration of memorized targets was selectively responsive to D_2-dopaminergic agents. In neuropsychological test settings, the different processing intercepts of these cycles are artificially amplified to assess the differing competencies of the PFC (e.g., compare the opposing features of tasks with a high load on working memory and attentional set shifting regarding stimulus rate, stimulus presentation time, and the employment of visually similar distractors). This might explain the observed receptor-dependent vulnerability profile in our study. Further empirical studies with adequate sample sizes are certainly necessary to confirm this suggestion.

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