Modulatory Effects of Levodopa on Cognitive Control in Young but not in Older Subjects: A Pharmacological fMRI Study

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Abstract

■ Older individuals show decline of prefrontal cortex (PFC) functions which may be related to altered dopaminergic neurotransmission. We investigated the effects of aging and dopaminergic stimulation in 15 young and 13 older healthy subjects on the neural correlates of interference control using fMRI. In a double-blind, placebo-controlled within-subject design, subjects were measured after levodopa (100 mg) or placebo administration. In each session, subjects performed a visual–spatial interference task based on a Stroop/Simon-like paradigm. Across age groups, interference (incongruent relative to congruent trials) was associated with activations in the presupplementary motor area, ACC, and intraparietal cortex. Increased interference was found behaviorally in older volunteers. Differential activation in left dorsolateral PFC in young subjects and bilateral PFC activity in older subjects was observed to be associated with interference control. Performance deteriorated under levodopa only in young subjects. This was accompanied by an increase of neural activity in ACC ($p < .05$; small-volume correction for multiple comparisons). Worsening of performance under levodopa in young subjects and the associated effect on ACC may indicate that overstimulation of the dopaminergic system compromises interference control. This supports the inverted-U-shaped model of neurotransmitter action. ■

INTRODUCTION

Aging is known to affect neurotransmitter systems in the human brain. Therefore, deterioration of cognitive functions in older age may depend, at least in part, on changes of neurochemical transmission (Piefke & Fink, 2005; Buckner, 2004; Backman et al., 1999). Evidence supporting this hypothesis has been shown, in particular, for memory (e.g., Wezenberg, Verkes, Sabbe, Ruigt, & Hulstijn, 2005; Daselaar, Veltman, Rombouts, Raaijmakers, & Jonker, 2003) and executive functions (Suhara et al., 1991). Deteriorating executive functions in older age have specifically been related to changes in the dopaminergic neurotransmitter system (Backman et al., 2000; Antonini & Leenders, 1993). Investigations in nonhuman primates (Goldman-Rakic & Brown, 1981), as well as behavioral and functional neuroimaging studies in humans (for reviews, see Rajah & D'Esposito, 2005; Buckner, 2004), converge on the view that the dopaminergic neurotransmitter system is affected by biological aging. Regions specifically affected by aging-related neurofunctional changes include dorsolateral PFC (DLPFC; Mitchell, Raye, Johnson, & Greene, 2006; D'Esposito, Kirkby, van Horn, Ellmore, & Berman, 1999) and anterior cingulate cortex (ACC; Sharp, Scott, Mehta, & Wise, 2006; Persson et al., 2004). These aging effects on the dopaminergic neurotransmitter system are based on changes in dopamine receptor densities, in the dopamine level, and in the activity of monoamine oxidase (MAO). A substantial decrease in the number of dopamine receptors was reported in prefrontal cortex (PFC; Suhara et al., 1991; de Keyser, De Backer, Vauquelin, & Ebinger, 1990). Further, decreased levels of dopamine were observed in the extrapyramidal nuclei, as well as frontal, temporal, and limbic cortices (Roth & Joseph, 1988). Finally, an increased activity of MAO-B and an increased dopamine catabolism were detected in the aging brain (Gottfries et al., 1983).

Executive functions are primarily mediated by PFC, which is a major target of dopaminergic projections from the midbrain (Hall et al., 1994). In addition, the nigrostriatal pathway innervates the basal ganglia, which also maintains connections with PFC. Individual dopamine abundance in the brain is supposed to be genetically determined (e.g., Mattay et al., 2003). An inverted U-shaped model has been suggested for neurotransmitter action in the brain (Thiel, Friston, & Dolan, 2002; Arnsten, 1997; Williams & Goldman-Rakic, 1995). This model predicts that dopaminergic stimulation facilitates executive performance in subjects with low-level dopamine abundance in PFC, but has a detrimental effect in individuals with high PFC dopamine levels (Mattay et al., 2000, 2003; Kimberg, D'Esposito, & Farah, 1997). An equivalent mechanism was demonstrated

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for the dopamine synthesis capacity in the striatum (Cools, Gibbs, Miyakawa, Jagust, & D'Esposito, 2008). It is not yet clear, however, how such determinants of dopaminergic neurotransmission may interact with dopaminergic decline in older age (Dreher, Meyer-Lindenberg, Kohn, & Berman, 2008; Ota et al., 2006).

In the present study, we investigated whether young and older volunteers differ in neural activity associated with interference control. A second issue we aimed to address was the effect of dopaminergic stimulation by levodopa on behavioral and neural correlates of interference in young and old subjects. The rationale for the choice of the cognitive task was based on the observation that cognitive control processes are associated with neural activity in ACC and PFC among other areas (Derrfuss et al., 2005; Laird et al., 2005; Bush, Luu, & Posner, 2000). A peak density-based approach analyzing neural activity evoked by different interference control tasks (47 neuroimaging studies) revealed ACC, DLPFC, inferior frontal gyrus, posterior parietal cortex, and anterior insula as common areas of activation (Nee, Wager, & Jonides, 2007). Another result of this meta-analysis was that if peak activations are mapped on a canonical brain, activations are distributed almost all over the brain depending on the task and the settings used. However, the resolution of interference itself seems to evoke a specific activity pattern in ACC and DLPFC among others. To focus primarily on the resolution of interference itself and to suppress other cognitive processes involved in these tasks, we have chosen a paradigm covering two interference tasks in one (Stroop-like and Simon-like interference). We hypothesized that the two age groups would show differential activation of DLPFC and ACC in response to interference. Based on the assumption that dopaminergic baseline levels decline during aging, we expected a benefit from dopaminergic stimulation in older individuals and a dysfunction under levodopa in young subjects (according to the inverted U-shaped model).

METHODS

Participants

Fifteen young (6 women; mean age ± *SD* = 24.23 ± 3.09 years) and 13 older (5 women; mean age ± *SD* = 63.81 ± 6.00 years) subjects, with no history of psychiatric, neurological, or other severe medical disorder, participated in the experiment. They had no history of drug or alcohol abuse and did not report a prior use of dopaminergic drugs. All subjects were right-handed, as assessed by the Edinburgh Inventory (Oldfield, 1971). Age groups were matched for sex, IQ, and level of education. The study was accomplished in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 2004). Written informed consent was obtained from all subjects prior to participation, and the local ethics committee approved the study.

Experimental Paradigm

The interference task used to assess inhibitory control processes was based on a visual–spatial Stroop/Simon-like paradigm devised by Liu, Banich, Jacobson, and Tanabe (2004). Stroop interference is associated with a stimulus–stimulus conflict (e.g., as in the classic color–word Stroop task; Stroop, 1935). By contrast, Simon interference induces a stimulus–response conflict (e.g., a conflict between left/right stimulus position and response with the left or right hand; for a discussion of the differences between Stroop and Simon interference, see Kornblum, 1992). In the present study, Stroop or Simon interference was induced by presenting a black arrow in an upward or downward direction either above or below (Stroop effect) or on the left or right side (Simon effect) of a fixation crosshair which was presented at the center of the screen (see Figure 1). Irrespective of the position of the arrow, the subjects were asked to press a response button with their left index finger when an upward arrow was presented, and with their right index finger when a downward arrow was presented. Eight different position–direction combinations (thereby constituting 8 different trial types) were possible. Half of the trial types induced a conflict (incongruent conditions; Stroop: downward arrow above, upward arrow below the fixation cross; Simon: upward arrow on the right, downward arrow on the left side of the fixation cross), the other half did not (congruent conditions; Stroop: upward arrow above, downward arrow below the fixation cross; Simon: downward arrow on the right, upward arrow on the left side of the fixation cross) (see Figure 1A).

Trials were presented in pseudorandom order. Each trial lasted 2076 msec, starting with a 500-msec fixation cross presentation, followed by the arrow stimulus for 100 msec, and ending with a response period for the remaining 1476 msec (see Figure 1B).

Each of the eight trial types was presented 45 times, leading to a total of 360 trials included in each fMRI session. Trials were intermingled with 180 null events, where only the fixation crosshair was shown. Each fMRI session lasted ≈19 min.

Screening of Subjects

The subjects included in the present pharmacological fMRI experiment participated in a more extended research project on genetic (catechol-*O*-methyltransferase [COMT] and apolipoprotein E [ApoE] genotypes) and aging-related factors, which modulate the neurochemical mechanisms of executive and memory functions. In the present experiment, COMT genotype was included into the analysis to control for group effects since previous studies reported significant effects of differential COMT genotypes on baseline executive performance (e.g., Mattay et al., 2003; Arnsten, 1997). Subjects underwent extensive neurological and psychiatric screening (e.g., for depression and dementia) as well as demographic and

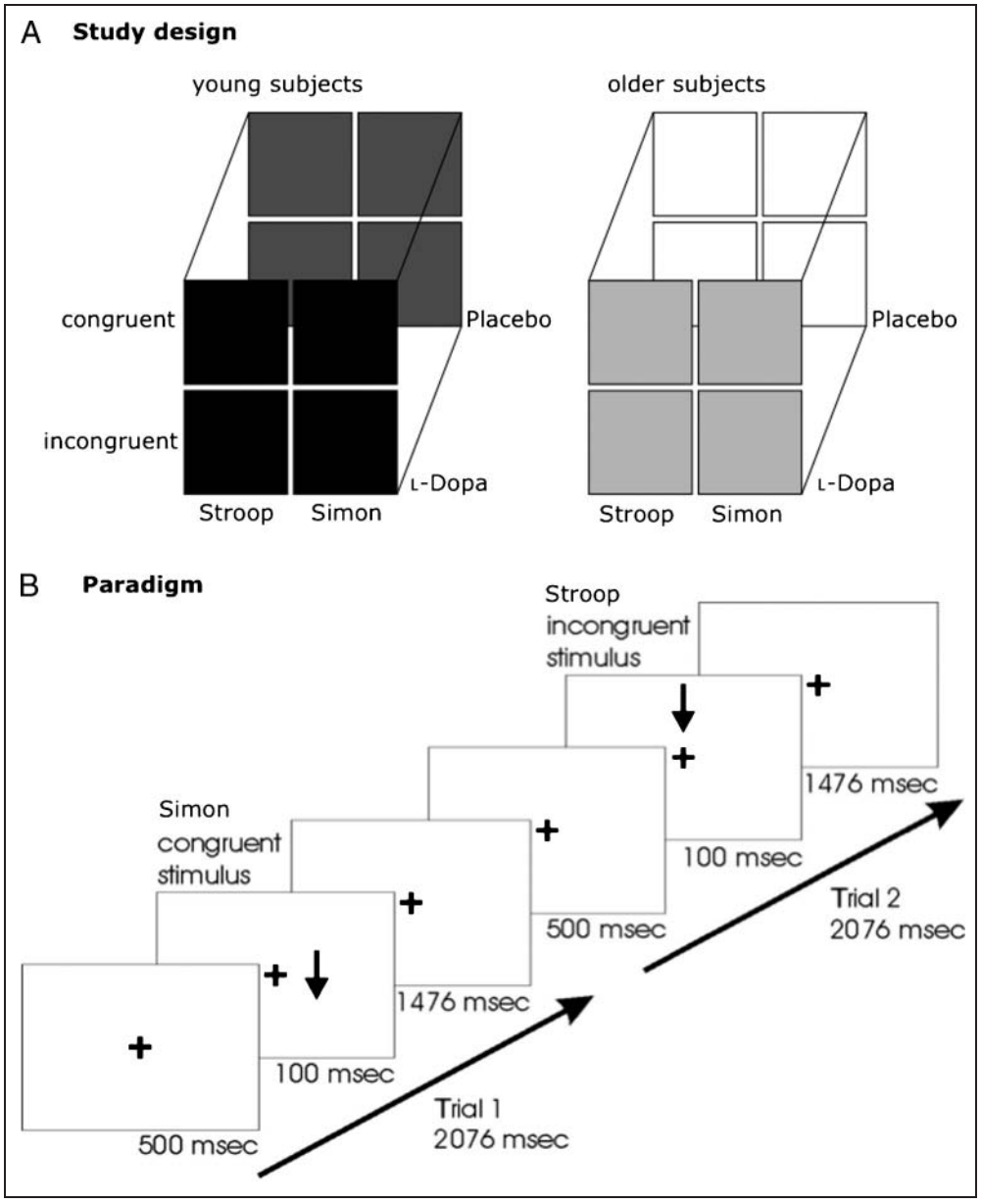

Figure 1. Stroop/Simon-like interference paradigm used to study inhibitory control functions in the present pharmacological fMRI experiment. (A) An interference paradigm including Stroop (stimulus–stimulus conflict) and Simon (stimulus–response conflict) conditions was used to study executive control processes in young and older subjects under two different experimental conditions with fMRI. Each participant underwent two fMRI sessions, one under levodopa, and another under placebo in counterbalanced order across subjects. (B) Congruent and incongruent Stroop or Simon interference trials alternated in pseudorandom order (2 × 2 factorial design). The subjects' task was always the same: They were asked to press a button with their right index finger in trials when a downward arrow was shown, and with the left index finger when an upward arrow was shown.

neuropsychological assessment (e.g., executive functions, memory, attention). These measures were used to exclude confounding medical conditions and to control for between-subject differences in demographic variables (e.g., level of education) and cognitive performance. Moreover, the participants were physically examined by a physician and, in particular, screened for levodopa contraindications.

Drug Administration

Each subject participated in two experimental fMRI sessions, which were separated by at least 7 days, but not longer than 14 days. fMRI measurements always took place at the same time during the day. Drug administration was double-blind, with counterbalanced order across subjects. Prior to each fMRI session, volunteers received either a capsule with a combination of levodopa (100 mg) and carbidopa (25 mg) (Nacom 100 mg, Bristol-Myers Squibb) or a placebo capsule with identical appearance. Forty-five minutes after drug administration, a blood sample was taken for later control of levodopa plasma level (reaching a maximum at 0.7 hr after ingestion with a concentration of 1091 ng/ml serum, the half life is 1.1 h; according to factual information by Bristol-Myers Squibb). Thereafter, the fMRI measurement was started.

Experimental Procedure

Heart rate and blood pressure were controlled before and after drug/placebo administration, at the end of each fMRI session and 45 minutes after the fMRI session to preclude pharmacologically induced changes of the

hemodynamic measures. Before entering the MR scanner, subjects performed a training block (10 min) to get familiarized with the Stroop/Simon interference task (see above) and to minimize training effects across fMRI sessions. Each fMRI session comprised two runs, one during which a working memory task was performed (data are not reported here) and one during which the described interference task was performed. The order of tasks was counterbalanced across subjects. After the fMRI measurement, subjects remained at least 45 min under the supervision of a physician to control for possible side effects of the drug. Meanwhile, subjects accomplished postscanning debriefing questionnaires on task performance during scanning (e.g., strategies used to accomplish the task) and were asked whether they thought that they had received the drug or a placebo. After the second experimental session, each subject was additionally interviewed in more detail about the strategies used during task performance.

Data Acquisition

A Sonata MRI System (Siemens, Erlangen, Germany) operating at 1.5 T was used to obtain T2*-weighted echoplanar (EPI) images with BOLD contrast (TR = 3.02, TE = 66 msec, matrix size: 64 × 64, pixel size: 3.125 × 3.125 mm^2, slice thickness = 4 mm, FOV = 200 mm, flip angle = 90°, 30 axial slices). The 30 slices covered a subject's brain from the cerebellar vermis up to the vertex and were oriented along the anterior–posterior commissure (AC–PC) line using a mid-sagittal scout image. Three hundred seventy-six volumes were acquired sequentially with a 0.4-mm gap. The first four volumes were discarded to allow for T1 equilibration effects.

A visual stimulation device (goggles; Silent Vision, Avotec, FL, USA) was used for stimulus presentation during the MR experiment, which was controlled by the software Presentation 0.76 (Neurobehavioral Systems, Albany, CA, USA; www.neuro-bs.com).

In addition, high-resolution anatomical MR images were acquired for coregistration with the functional scans (T1-weighted 3-D MP-RAGE) and to control for aging-related brain atrophy, white matter lesions, and macroangiopathy (T2-weighted FLAIR and Time of Flight measurements in the older subjects only).

Data Analyses

Behavioral Data

Behavioral data were analyzed with repeated measures ANOVAs with the factors age group, pharmacological challenge, and interference effect (as indicated by the reaction times in incongruent trials minus reaction times in congruent trials). The statistical threshold applied to all behavioral data was $p < .05$ (one-tailed), corrected for multiple comparisons according to the Bonferroni inequality.

Neuroimaging Data

Statistical Parametric Mapping (SPM2, Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB 6.5 (Mathworks, Sherborn, MA, USA) was used for image processing and statistical analysis. Images were spatially realigned to the first volume to correct for head movements, interpolated in time (temporal realignment to the middle slice), and normalized to an EPI template volume in standard stereotactic MNI (Montreal Neurological Institute) space. For spatial smoothing, an isotropic Gaussian kernel of 8 mm (full-width half-maximum) was used to compensate for normal variations in brain size and individual gyral patterns. A high-pass filter with a cutoff frequency of 1/128 Hz was used to eliminate noise in the low-frequency range.

Statistical analysis of the fMRI data was conducted using a mixed-effects model. At the single-subject level (first level), a design matrix comprising the eight events of interests and movement parameters was created for each subject. Congruent and incongruent conditions were modeled by means of reference waveforms corresponding to stick functions which were placed at the onset of the stimuli convolved with a hemodynamic response function (Friston, Ashburner, et al., 1995; Friston, Holmes, et al., 1995). Specific effects were assessed by applying appropriate linear contrasts to the parameter estimates of the experimental trials resulting in t statistics for each voxel. These formed statistical parametric maps (SPM{T}) of differences between the conditions. Age- and drug-specific effects on brain activation associated with task performance were assessed on the between-subject level ("second level"). For each simple effect (i.e., incongruent Simon trial in young subjects under levodopa challenge) of either session, individual contrast images of each subject were entered into an ANOVA model (mixed design, between-subjects effects for factor age, within-subject effects for factor drug).

To analyze brain activations common to the two age groups and/or interference types (Stroop/Simon), conjunction analyses were performed based on the global null hypothesis ($k \geq 1$) (Friston, Penny, & Glaser, 2005). The underlying contrasts used to perform the conjunction analyses were incongruent versus congruent trials for the respective groups or interference types. Due to the predicted small effect size and the character of the analysis (second level analysis based on a random effects model), a height threshold of $p < .001$ (uncorrected) and an extent threshold of (larger than) 5 voxels were accepted to prevent type I errors (MacAvoy, Ollinger, & Buckner, 2001; Forman et al., 1995). Additionally, small-volume correction (radius 20 mm) for multiple comparisons ($p < .05$; familywise error) was performed using literature-based coordinates (meta-analysis by Nee et al., 2007). Coordinates

of interest were derived by a peak density-based analysis combining multiple tasks requiring the resolution of interference.

RESULTS

Behavioral Data

Error Rates and Reaction Times

Responses during performance of the interference task were analyzed for differences (i) in error rates and reaction times between congruent and incongruent conditions, (ii) between age groups, and (iii) between the levodopa and placebo fMRI sessions.

Across age groups and sessions, the mean error rate was 6.54 (SD = ±6.19) in congruent trials and 13.54 (SD = ±10.73) in incongruent trials. This difference was significant [ANOVA, factor congruency; $F(1, 26) = 38.932$, $p < .001$]. The analysis showed that age groups did not differ from each other significantly [ANOVA, factor group; $F(1, 26) = 0.199$, $p = .330$]. Also, Drug × Congruency × Group interactions were nonsignificant [$F(1, 26) = 0.070$, $p = .397$] (Figure 2A).

A repeated measures ANOVA on reaction times with age group as between-group factor revealed a statistically significant main effect of Incongruency (effect of combined Stroop and Simon interference) with significantly longer reaction times for incongruent than congruent trials [ANOVA, factor incongruency; $F(1, 26) = 118.433$, $p < .001$] as well as a significant Interference × Age interaction [$F(1, 26) = 16.433$, $p < .001$]. The "interference effect" (given by the reaction times in incongruent trials minus reaction times in congruent trials) was significantly higher in older (48.2 ± 22.2 msec) than in younger (22.0 ± 10.8 msec) subjects. The repeated measures ANOVA with the between-group factor age and the within-group factor pharmacological challenge missed statistical significance, but revealed a trend toward an omnibus interaction effect [ANOVA, factor age and pharmacological challenge; $F(1, 26) = 1.862$, $p = .092$].

Repeated measures ANOVAs with the pharmacological challenge as the within-group factor yielded an increased difference between reaction times in incongruent and congruent trials in the levodopa session for the young group only [ANOVA, factor pharmacological challenge; $F(1, 14) = 4.032$, $p = .032$] (Figure 2B). The change of the difference was based on an absolute increase of reaction time in incongruent trials (from 620.6 ± 85.3 msec in the placebo session to 633.4 ± 93.3 msec in the levodopa session), whereas the reaction time for the congruent trials remained constant across sessions (604.2 ± 92.7 msec in the placebo session, 605.7 ± 88.1 msec in the levodopa session). These effects were observed in all conditions, irrespective of the type of interference (Stroop- vs. Simon-like). In the older subjects, no significant differences were evident on the group level [ANOVA, factor pharmacological challenge; $F(1, 12) = 0.025$, $p = .439$].

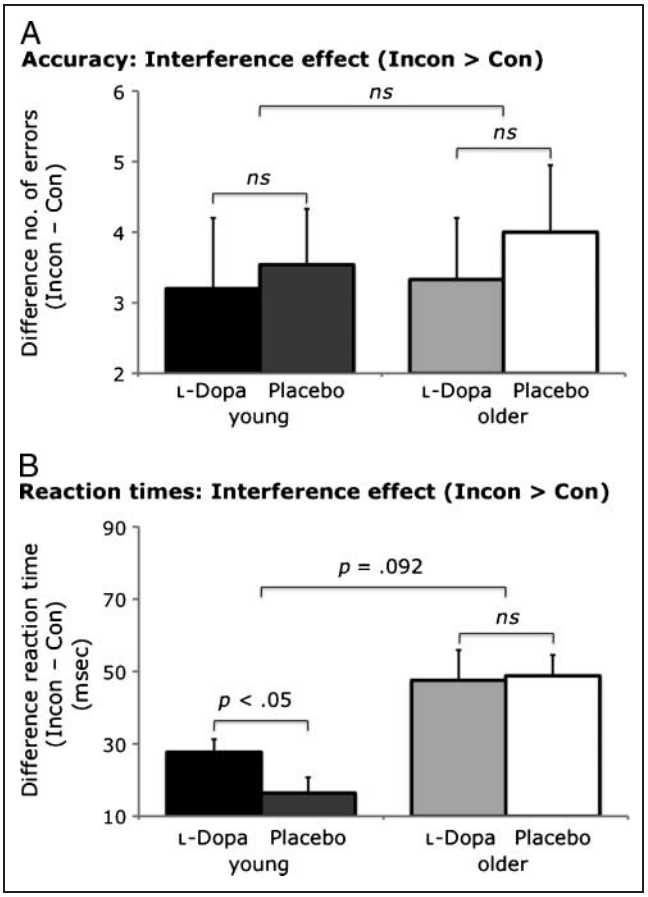

Figure 2. Differences in reaction times and accuracy of task performance between congruent and incongruent conditions in young and older volunteers for the levodopa and the placebo sessions. (A) Incongruent (relative to congruent) trials increased significantly error rates in both young and older participants with no statistically significant differences between age groups and drug and no significant Group × Drug interactions. (B) The interference effect was higher in older as compared to younger volunteers. Within the young group, an increased interference effect was found in the levodopa session. The repeated measures ANOVA (factors age and pharmacological challenge) missed statistical significance, but revealed a trend toward an omnibus interaction effect.

There were no significant effects of single subjects' COMT genotypes (val/val, val/met, met/met) and levels of behavioral performance [ANOVA, factor genotype; $F(2, 24) = 1.285$, $p = .147$]. Table 1 details individual changes of performance in response to levodopa administration, as well as each participant's COMT genotype.

No training effects were observed between the first and the second fMRI sessions, irrespective of the order of drug and placebo sessions.

Neuropsychological Data

The Number-Span Task (Wechsler Adult Intelligence Scale; Wechsler, 1997) as a working memory related task was performed independently from the fMRI paradigm. The young subjects relative to the older subjects performed

Table 1. Individual Differences in Task Performance in Response to Levodopa and COMT Genotype

Age Group	*Subject No*	*Sex*	*Interference Effect (msec)*	*Standard Error*	*COMT Genotype*
Young	1	m	13.51	15.15	val/val
Young	2	f	−25.17	18.96	val/val
Young	3	m	27.27	27.39	val/val
Young	4	m	13.59	24.00	val/met
Young	5	m	−0.94	24.37	val/met
Young	6	m	22.37	29.74	met/met
Young	7	f	−3.99	9.54	met/met
Young	8	m	35.77	30.59	met/met
Young	9	m	6.82	8.66	val/met
Young	10	f	5.68	19.08	val/met
Young	11	f	−16.63	15.67	val/met
Young	12	m	11.38	9.20	met/met
Young	13	m	36.02	19.72	val/met
Young	14	f	−14.42	19.06	val/met
Young	15	f	51.23	27.44	val/met
Old	1	f	39.23	23.64	val/met
Old	2	m	13.57	28.98	met/met
Old	5	m	27.98	18.79	val/met
Old	6	f	11.78	17.92	val/met
Old	7	f	20.31	19.41	met/met
Old	8	m	4.26	17.47	met/met
Old	9	m	−24.41	16.47	val/val
Old	10	m	−20.30	10.18	missing
Old	11	m	−38.59	26.25	met/met
Old	12	m	4.15	17.23	met/met
Old	13	m	−45.94	28.61	val/val
Old	14	f	−17.55	24.38	val/met
Old	16	f	13.43	14.28	val/val

Interference effect = levodopa session (incon − con) − placebo session (incon − con). A negative value for the interference effect indicates improvement, whereas a positive value indicates a decline under levodopa.

incon = incongruent conditions; con = congruent conditions; val/val = COMT homozyguous valine genotype; met/met = COMT homozygous methionine genotype; val/met = COMT heterozygous valine/methionine genotype; m = male; f = female.

significantly better in the subtask demanding a high workload (digits forward, young group, mean = 8.67, $SD = \pm 1.95$, older group, mean = 7.58, $SD = \pm 1.62$, $p = .12$; digits backward, young group, mean = 8.87, $SD = \pm 3.00$, older group, mean = 6.42, $SD = \pm 1.73$, $p = .01$).

Postscanning Debriefing Procedures

Across age groups, participants subjectively indicated a low level of task difficulty. On a rating scale from 1 ("very easy") to 5 ("very difficult"), the mean value given by the volunteers was 1.91 ($SD = \pm 0.47$). In the young group, the mean rating of task difficulty was 1.73 ($SD = \pm 0.51$), in the older it was 2.09 ($SD = \pm 0.37$). A Mann–Whitney U-test showed that the between-group difference reached statistical significance ($Z = -2.475$; $p = .013$). Across age groups, participants rated incongruent trials (mean = 2.00, $SD = \pm 0.50$) significantly more difficult than congruent ones (mean = 1.81, $SD = \pm 0.45$; Wilcoxon test; $Z = -3.084$; $p = .002$).

In the young group, the difference of the ratings of the incongruent and congruent conditions was significant for the levodopa session (Wilcoxon test; $Z = -2.585$; $p = .01$), but failed to reach statistical significance for the placebo session (Wilcoxon test; $Z = -1.841$; $p = .066$). In the older group, neither for the levodopa (Wilcoxon test; $Z = -1.511$; $p = .131$), nor the placebo session (Wilcoxon test; $Z = -1.134$; $p = .257$), rating of task difficulty for incongruent and congruent conditions differed from each other.

Physiological Measures/Side Effects

There were no significant differences in heart rate or blood pressure across the whole experimental procedure for both the levodopa and the placebo sessions. None of the subjects reported adverse side effects of the drug. Importantly, correctness of the participants' judgment whether they had received the drug or placebo in each session was at chance level (young subjects 46.7%, older subjects 53.8% correct judgment).

Neuroimaging Data

We here focus on the main effect of interference on brain activation (i.e., the neurofunctional changes associated with incongruent and congruent conditions) and aging- and drug-related differences in brain activation associated with this contrast.

Common Activations for the Age Groups and the Interference Type (Irrespective of Drug)

Common activations in both age groups (irrespective of drug and interference type) were gauged by a conjunction analysis. The common neural circuit activated by the main effect of incongruency (incongruent vs. congruent) across sessions (drug and placebo) included the presupplementary motor area (pre-SMA), ACC, left intraparietal cortex (IPC) and additional small areas of frontal cortex (left precentral gyrus, right inferior frontal gyrus (IFG) [pars orbitalis]), parietal cortex (right precuneus), and left insula (see Figure 3A and Table 2). Another conjunction analysis comprising common activations for both types of interference, namely, Stroop- and Simon-like task (irrespective of drug and group), showed a very similar pattern (see Figure 3B and Table 2).

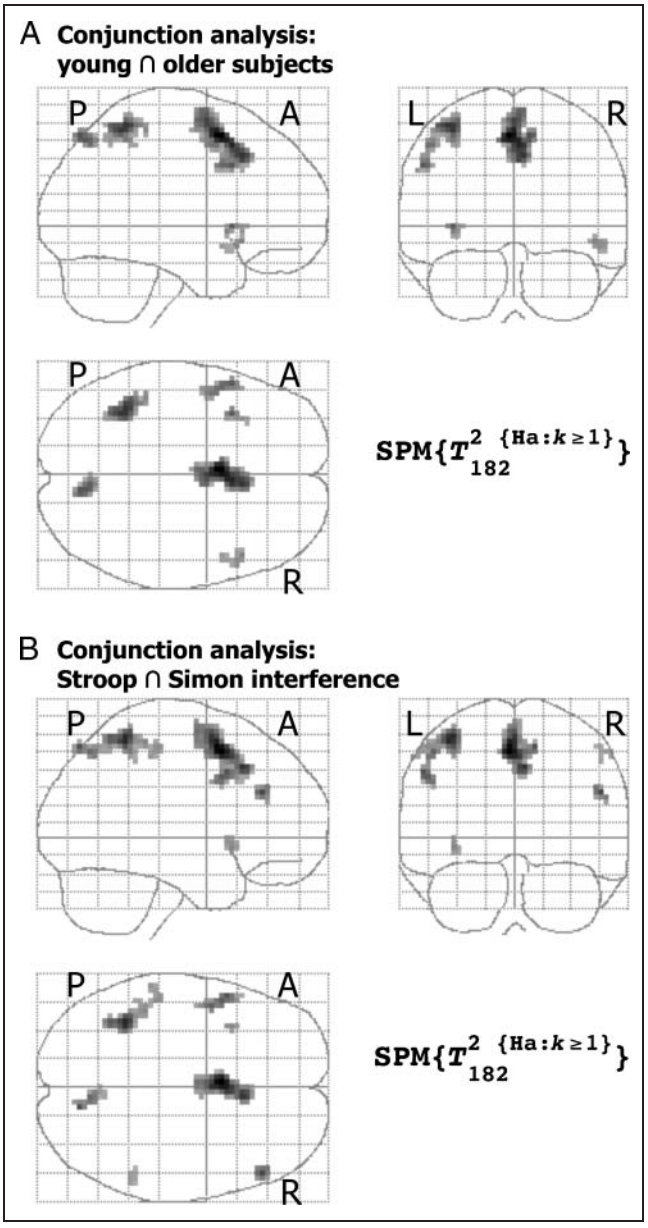

Figure 3. Brain activation associated with the contrast between incongruent and congruent conditions common to the two age groups and common to both types of interference (irrespective of drug; conjunction analyses). (A) Common activations in young and older participants (irrespective of Stroop or Simon interference and drug) were observed in the pre-SMA, ACC, and IPC, as well as in frontal and parietal regions. (B) The conjunction analysis for both types of interference reveals a similar pattern. Height threshold of $p < .001$ (uncorrected for multiple comparisons).

Age-related Differences in Brain Activation

In young subjects, brain activity associated with incongruent (relative to congruent) conditions (irrespective of Stroop or Simon interference) was observed in the left pre-SMA (extending into ACC), left DLPFC, left IPC, the right insula, and the right temporal pole (see Table 3 and Figure 4A). The equivalent contrast for the group of older subjects yielded neural activations in the inferior frontal gyrus (IFG) bilaterally, pre-SMA, and ACC, as well as left IPC (see Table 3 and Figure 4B). Involvement of left DLPFC (young group) and left IFG (old group) differed significantly between the age groups (Condition × Group interaction). Figure 4C details these aging-related

Table 2. Conjunction Analysis of Relative Increases in Brain Activity Associated with Incongruent (Relative to Congruent) Conditions in Young and Older Subjects (Irrespective of Interference Type and Drug) and in Stroop and Simon Interference (Irrespective of Age and Drug)

Conjunction	*Region*	*Side*	*x*	*y*	*z*	*t*
Young ∩ Older subjects	Pre-SMA	L	−3	9	54	4.11
		R	3	15	48	3.40
	ACC	R	6	21	42	3.20
	IPC	L	−39	−48	60	3.18
	Precuneus	R	9	−75	54	2.85
	Precentral Gyrus	L	−54	15	36	2.77
	Insula	L	−36	15	0	2.71
	IFG	R	48	21	−9	2.30
Stroop ∩ Simon interference	Pre-SMA	L	−3	9	51	4.28
	ACC	R	6	21	42	3.29
	IPC	L	−39	−48	57	3.44
	IFG	R	51	33	27	3.05
	Precuneus	R	12	−75	54	2.97
	Precentral Gyrus	L	−54	12	39	2.89
	Insula	L	−36	15	−6	2.32
	Inf. Parietal Gyrus	R	54	−45	51	2.03

Activations significant at $p < .001$, uncorrected for multiple comparisons.

x, distance (mm) to right (+) or left (−) of the mid-sagittal plane; *y*, distance anterior (+) or posterior (−) to vertical plane through the anterior commissure; *z*, distance above (+) or below (−) the intercommissural (AC–PC) plane in standard stereotactic MNI space. ACC = anterior cingulate cortex; IFG = inferior frontal gyrus; Inf = inferior; IPC = intraparietal cortex; L = left; R = right; SMA = supplementary motor area.

differences in PFC activations in respect to the relative signal change.

Drug-related Differences in Brain Activation

Drug-specific effects on brain activation during processing of incongruent trials could be seen in the young group only: In the levodopa (relative to the placebo) session, a Drug × Congruency interaction was observed in ACC (MNI coordinates $x\ y\ z = 6, 27, 39$ mm). This was evident in a higher response to incongruent than to congruent trials. The reverse contrast (placebo vs. levodopa session) did not show any suprathreshold activations. In older subjects, no drug-specific effects on brain activation were observed.

Age-by-Drug Interactive Relation in Brain Activation

The three-factorial interaction contrast (Age group × Drug challenge × Condition) masked by the congruency main effect revealed a significant difference between levodopa action in young and older volunteers in ACC (MNI coordinates $x\ y\ z = 3, 30, 39$ mm, $p = .047$, small-volume correction for multiple comparisons) (see Figure 5).

DISCUSSION

We here demonstrate neurofunctional changes depending on the interference effect associated with a Stroop/Simon-like paradigm. Across age groups, incongruent (relative to congruent) trials were associated with differential activations mainly in the pre-SMA, ACC, and IPC. Aging-related differences associated with interference conditions were observed in left DLPFC with stronger activity in young subjects, and in the left IFG with increased activity in older subjects. Under levodopa, we observe an increase in the interference effect behaviorally, an increase of subjectively experienced task difficulty in young subjects, and an increased ACC activity.

One important consideration in this context is the differentiation between specific activity changes in the ACC region as opposed to nonspecific levodopa effects resulting from homogeneous changes in cerebral hemodynamics. Based on previous research using pharmacological challenges in the dopaminergic neurotransmitter system (either

enhancing or blocking) (Dodds et al., 2008), one would not expect global effects. Even changes in cerebral blood flow were not associated with a modulation of the BOLD signal (Gollub et al., 1998).

The pre-SMA, ACC, and IPC have previously been related to the cognitive control of interference (Laird et al., 2005; Liu et al., 2004). Our finding of differential activation of these regions associated with incongruent relative to congruent conditions (irrespective of interference type, age, and drug) is in good accordance with these neuroimaging data.

ACC activity may reflect multiple facets underlying the control of conflict. Suggested ACC functions include attentional control (Posner, 1994), monitoring, detection, and resolution of conflict (Barch et al., 2001), as well as response selection (Stephan et al., 2003), error processing (Schultz, 2006; Brown & Braver, 2005), monitoring competition, and complex motor control (Bush et al., 2000). There is some evidence based on EEG data that dopaminergic signaling to ACC enables us to adjust behavior and to modify task performance (Holroyd & Coles, 2002). It is therefore unlikely that specific response requirements of

Table 3. Relative Increases in Brain Activity Associated with Incongruent Relative to Congruent (INCON > CON) Conditions in Young and Older Subjects Separately (Irrespective of Verum and Task) and in the Interaction Contrast (Condition-by-Group)

(A) Activations Significant at $p < .001$, Uncorrected for Multiple Comparisons

Contrast	*Region*	*Side*	*k*	*x*	*y*	*z*	*t*
(Incon > Con) in young	Pre-SMA/ACC	L	67	−3	6	57	4.37
	DLPFC	L	16	−33	57	9	4.15
	IPC	L	10	−36	−48	60	3.86
	Insula	R	9	39	21	−9	3.82
	Temporal pole	R	8	27	6	−18	4.20
(Incon > Con) in older	Pre-SMA	L	42	−3	9	51	5.34
	IFG (at the IFJ)	L	23	−48	6	30	4.28
	IPC	L	19	−39	−48	57	3.98
	IFG	R	11	51	33	27	4.13
	ACC	R	10	6	21	42	3.66
	Precuneus	R	9	6	−69	51	3.40
	Insula	L	7	−36	18	−3	4.00
(Incon > Con) in young > (Incon > Con) in older	Temporal pole	R	10	27	6	−18	3.98
	DLPFC	L	9	−33	54	12	3.82
	Lingual gyrus	R	7	15	−45	−3	3.81
	Cuneus	L	6	−12	−81	18	3.44
(Incon > Con) in older > (Incon > Con) in young	IFG (at the IFJ)	L	5	−48	6	27	3.60

(B) Activations Significant at $p < .05$; Small-volume Correction, Corrected for Multiple Comparisons (Family-wise Error)

Contrast	*Region*	*Side*	*k*	*x*	*y*	*z*	*p*
(Incon > Con) in young	Pre-SMA/ACC	L	61	−3	6	57	.013
(Incon > Con) in older	Pre-SMA	L	42	−3	9	51	.000
	IFG (at the IFJ)	L	23	−48	6	30	.018
	IPC	L	19	−39	−48	57	.047
	IFG	R	11	51	33	27	.029
(Incon > Con) in young > (Incon > Con) in older	No suprathreshold clusters						
(Incon > Con) in older > (Incon > Con) in young	No suprathreshold clusters						

DLPFC = dorsolateral prefrontal cortex; IFJ = inferior frontal junction; Incon = incongruent; Con = congruent.

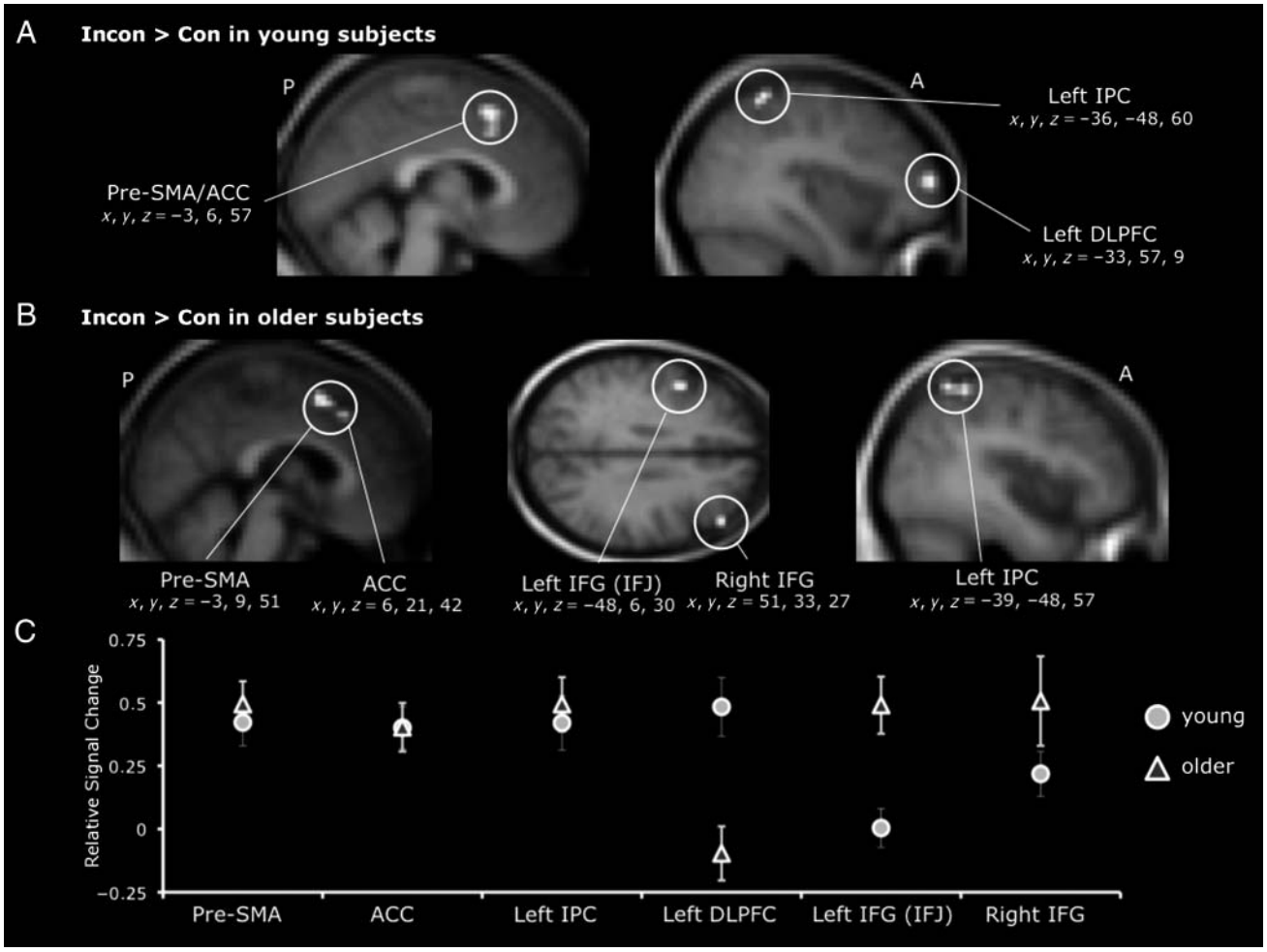

Figure 4. Brain activation in young and older subjects for the contrast between incongruent and congruent conditions (irrespective of interference type and verum). (A) Differential activations in young subjects for the contrast between incongruent and congruent conditions were observed in the pre-SMA/ACC**, DLPFC*, and IPC* in the left hemisphere. (B) Older volunteers differentially recruited the IFG in the right** and the left* hemispheres, the pre-SMA**, and IPC** in the left hemisphere, as well as right ACC*. (C) Relative BOLD signal change of the local maxima for the relevant brain regions indicates that both age groups recruited the pre-SMA, ACC, IPC, and right IFG in response to interference-related incongruent (relative to congruent) trials. In contrast, involvement of left DLPFC (young group) and left IFG (old group) differed between age groups (see also Table 3A). Height threshold of $*p < .001$ (uncorrected for multiple comparisons) and $**p < .05$ (small-volume correction for multiple comparisons).

the Simon task can account for the lack of ACC activation during Stroop interference trials as argued in the study by Liu et al. (2004). Our results show ACC activity in response to both types of interference (Figure 3B). ACC closely interacts with lateral prefrontal areas in executive processes. These regions are supposed to mediate top–down support of task-appropriate behavior while ACC has rather been implicated in evaluative processes (e.g., when control needs to be strengthened; MacDonald & Joordens, 2000). Neuroimaging studies of inhibitory control corroborate this view, demonstrating that ACC activity is correlated with increasing evaluative task demands (Kerns et al., 2004; Bush et al., 1998). It is reasonable to assume that, in our study, incongruent (relative to congruent) trials were associated with higher demands on the evaluation of efficient control (rather than top–down control itself). Therefore, the suggested ACC involvement in evaluative processes is supported by our current data showing interference-related differential ACC activation. The view of Botvinick, Nystrom, Fissell, Carter, and Cohen (1999) postulating that ACC is involved in continuous monitoring rather than the top–down attentional control of conflict also agrees with this interpretation.

The drug-specific effect on ACC and the associated worsening of performance in young subjects may indicate that levodopa administration caused overstimulation of the dopaminergic system, yielding PFC dysfunction. Given that ACC is involved in the monitoring of control processes, it is likely that increased activity of this region under levodopa reflects enhanced cognitive control effort to cope with the interference conditions during levodopa challenge. In another study with the same drug in the same dose, an instrumental learning task was performed with a group of healthy young subjects in a similar age

range (Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006). In that study, an improved performance under levodopa was demonstrated. However, in that task, feedback was given, and thus, prediction error was involved. Both studies suggest that dopaminergic stimulation may show an interesting dissociation on two different anatomical–functional systems, namely, the reward-based learning system underpinned by the ventral striatum and the cognitive control system underpinned by PFC.

In contrast to the young subjects, the older subjects showed no significant drug-associated effect both in task performance and in neural activity. This differential response to the levodopa challenge can be explained by the inverted U-curve model, predicting that overstimulation of the dopaminergic system causes executive dysfunction (e.g., Mattay et al., 2003). In healthy young individuals, dopaminergic neurotransmission is presumably intact such that the levodopa challenge increased PFC dopamine levels above optimum and led to worsened task performance. In contrast, in the older volunteers, baseline PFC dopamine levels might have already declined due to biological aging. One can therefore argue that levodopa administration did not yield a hyperdopaminergic state in the old group and, therefore, performance of the older subjects did not become worse under the drug (Volkow et al., 2000). In this context, one should, however, keep in mind that dopamine receptors may be altered in older age (Suhara et al., 1991), that overall dopamine levels in the aging brain are reduced (Roth & Joseph, 1988), that activity of monoamine oxidase is increased (Gottfries et al., 1983), and that levodopa could therefore induce effects in older individuals that may be different from those elicited in young adults. Furthermore, using a levodopa challenge does not take into account the differential influences of mesocortical D_1 and D_2 receptors in PFC (Tost et al., 2006). Further investigation is needed on whether overstimulation of the dopaminergic systems leads to selective dysfunctions of monitoring, control, or other executive processes related to ACC.

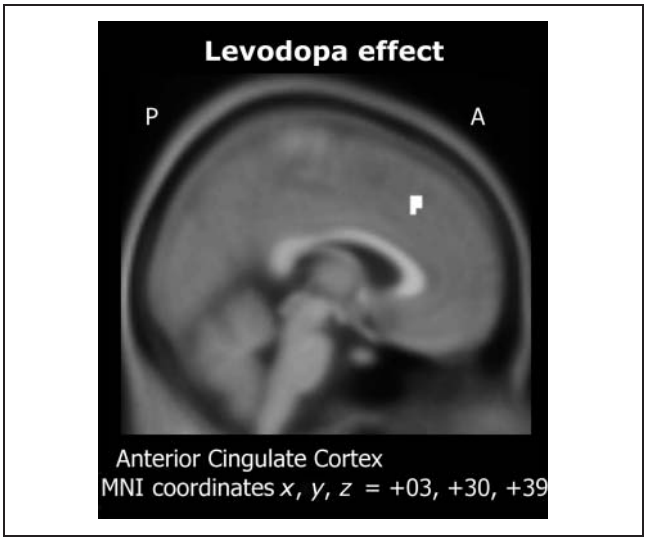

Figure 5. Drug-dependent differential brain activation in young (relative to older) subjects during the levodopa (relative to the placebo) session for incongruency. In young subjects, the dopaminergic challenge induced differential activation of right ACC during the performance of incongruent trials [contrast: levodopa > placebo in young subjects]. In the older subjects, no drug-specific effects on brain activation were observed [contrast: levodopa > placebo in older subjects]. The interaction contrast between both age groups revealed a neural activity in ACC as presented in the figure above [contrast: (levodopa > placebo in young subjects) > (levodopa > placebo in older subjects)]. Height threshold of $p < .05$ (small-volume correction for multiple comparisons).

Contrary to our primary expectation, dopaminergic enhancement did not improve task performance in the older subjects on the group level. Possibly, administration of higher single doses of levodopa or long-term treatment with levodopa is required to improve cognitive control capacity in older individuals. Single-subject analyses, however, revealed individual improvement of task performance under the drug in both groups (see Table 1). These findings suggest that interindividual differences in PFC dopamine levels and/or responses to levodopa have to be taken into account. This aspect is consistent with a previous pharmacological study of working memory (WM), indicating that subjects with low-level baseline WM performance profit from administration of a dopamine agonist, whereas subjects with high-level baseline performance do not (Mattay et al., 2000; Arnsten, 1997). In our study, we observed a high-level baseline WM for the young group, whereas the old group performed on a lower baseline WM level. The levodopa challenge might cause only a minor shift up the ascending limb of the inverted U-curve in the old group, whereas a more significant shift onto the descending limb occurs in the young group. Baseline WM and other executive abilities may be determined by genetic factors: Mattay et al. (2003) postulated that the COMT val^{158}–met polymorphism determines interindividual variability in executive performance and responses to dopaminergic stimulation. In their study, individuals with homozygous val/val genotype (characterized by low PFC dopamine levels) had low baseline executive performance and benefited from stimulation by amphetamine. By contrast, subjects with homozygous met/met genotype (characterized by high PFC dopamine levels) showed high baseline executive performance and did not benefit from amphetamine stimulation. However, several studies failed in replicating similar results and an extensive meta-analysis revealed no associations between the COMT polymorphism and several cognitive tasks such as the trail making task, verbal recall, verbal fluency, *n*-back task, and the Wisconsin Card Sorting Test (Barnett, Scoriels, & Munafò, 2008). Solely robust but small associations were observed between the genotype and IQ score, for which the most data, and thus, the strongest statistical power were present. Due to rather small genotype subgroups (especially homozygote subgroups), a correlation between COMT genotypes and levels of task performance could not be performed. However, we used the data to control and exclude genetic effects causing group differences.

The data provide a neurofunctional basis for the observation that task performance was cognitively more effortful for older than young subjects. There was increased brain activity in left DLPFC during the performance of incongruent (vs. congruent) trials in young subjects, whereas the same contrast revealed differential activation of the IFG in the older subjects. Interference-related left DLPFC activation in the young, but not the old, group is in accordance with the view that this PFC region mediates efficient inhibitory control (Langenecker, Nielson, & Rao, 2004), monitoring and cognitive strategies in WM (Rypma, Berger, & D'Esposito, 2002) and other executive functions (Rypma, Eldreth, & Rebbechi, 2007; Milham et al., 2002). Studies on cognitive control in healthy aging yield alterations in the maintenance of goal-relevant information rather than a deficit in inhibitory control (Paxton, Barch, Racine, & Braver, 2008; Braver & Barch, 2002). IFG recruitment in the older group (in the absence of DLPFC activation) might reflect compensatory brain activation (e.g., substitutional IFG recruitment due to aging-related DLPFC dysfunction) and/or a functional reorganization associated with older age (e.g., prefrontal functional reorganization due to aging-related neurochemical changes). The IFG (in particular, the inferior frontal junction) has been implicated in the updating of task-relevant information during executive processing (Derrfuss, Brass, & von Cramon, 2004) and with cognitive control performing response inhibition (Forstmann et al., 2008).

The pre-SMA is a known mediator of higher-order motor control (Picard & Strick, 1996). Given that the pre-SMA maintains strong connections to PFC, it is not surprising that this region is also involved in interference tasks (Zysset, Muller, Lohmann, & von Cramon, 2001; Hazeltine, Poldrack, & Gabrieli, 2000). Our data support this view. More importantly, they also suggest that this brain area is relatively unaffected by biological aging because there was a comparable interference effect on pre-SMA activation in both young and older subjects.

The area in IPC which was differentially activated by interference conditions in the present study is part of a fronto-parietal circuit involved in higher-order attentional processing (e.g., Corbetta & Shulman, 2002; Grefkes, Weiss, Zilles, & Fink, 2002). This network primarily mediates top–down control of attention. Our finding of interference-related differential IPC activation might thus reflect increased attentional top–down control required by conflict monitoring and response selection.

Limitations of the study are the relatively low field strength of the MRI system (1.5 T), the relatively small effects sizes, the statistical thresholds used, and the small cluster extent threshold. The size of the drug effects could be further refined by employing MRI systems with filed strengths of 3 T or higher. Another limitation is that the omnibus interaction effect on behavioral level (factors group, pharmacological challenge, and congruency) reveals a trend to significance only, whereas this contrast gets significant for our neuroimaging data. The issue of how to interpret changes in neural activity in the absence of significant behavioral effects (or trend to significance) has been raised previously and there is evidence to assume that neural data acquired with fMRI might be more sensitive than behavioral data as changes in cognitive effort are not necessarily reflected in behavioral measures such as correct response rates or reaction times (Wilkinson & Halligan, 2004; Fink, Marshall, Weiss, Toni, & Zilles, 2002).

In summary, the finding that performance became worse under levodopa in young, but not older, subjects is in good accordance with the inverted U-curve model of neurotransmitter action in the brain. The corresponding drug effect on ACC activation in young subjects suggests that overstimulation of the dopaminergic system may compromise PFC functions, in particular, the monitoring of cognitive control.

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