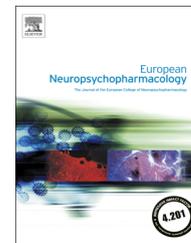




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The role of dopamine in inhibitory control in smokers and non-smokers: A pharmacological fMRI study



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Abstract

Contemporary theoretical models of substance dependence posit that deficits in inhibitory control play an important role in substance dependence. The neural network underlying inhibitory control and its association with substance dependence have been widely investigated. However, the pharmacology of inhibitory control is still insufficiently clear. The aims of the current study were twofold. First, we investigated the role of dopamine in inhibitory control and associated brain activation. Second, the proposed link between dopamine and impaired inhibitory control in nicotine dependence was investigated by comparing smokers and non-smoking controls. Haloperidol (2 mg), a dopamine D2/D3 receptor antagonist, and placebo were administered to 25 smokers and 25 non-smoking controls in a double-blind randomized cross-over design while performing a Go/NoGo task during fMRI scanning. Haloperidol reduced NoGo accuracy and associated brain activation in the ACC, right SFG and left IFG, showing that optimal dopamine levels are crucial to effectively implement inhibitory control. In addition, smokers showed behavioral deficits on the Go/NoGo task as well as hypoactivity in the left IFG, right MFG and ACC after placebo, supporting the hypothesis of a hypoactive prefrontal system in

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smokers. Haloperidol had a stronger impact on prefrontal brain activation in non-smoking controls compared to smokers, which is in line with the inverted 'U' curve theory of dopamine and cognitive control. The current findings suggest that altered baseline dopamine levels in addicted individuals may contribute to the often observed reduction in inhibitory control in these populations.

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1. Introduction

Contemporary theoretical models of substance dependence posit that deficits in inhibitory control are of key importance in the development and continuation of substance dependence (Goldstein and Volkow, 2011; Jentsch and Taylor, 1999; Lubman et al., 2004). Deficits in inhibitory control may contribute to the inability to stop taking drugs despite negative consequences and may increase reactivity to substance related cues including attentional bias (Field and Cox, 2008). Inhibitory control is accomplished through a cortical-striatal-thalamic network with feedback loops from sub-cortical regions such as the basal ganglia to prefrontal regions (Feil et al., 2010). The cortical part of the inhibitory control network is mainly right-lateralized and includes the inferior frontal gyrus (IFG), the anterior cingulate gyrus (ACC)/pre-supplementary motor area (pre-SMA) and dorso-lateral prefrontal cortex (DLPFC), as well as parietal areas (Aron and Poldrack, 2006; Chambers et al., 2009; Swick et al., 2011). Hypoactivation in prefrontal brain regions has been reported in substance dependent individuals including smokers (De Ruiter et al., 2012; Hester and Garavan, 2004; Kaufman et al., 2003; Li et al., 2009; Nestor et al., 2011). Additionally, hypoactivation in these regions seems to be related to difficulties in controlling substance use in daily life as it was found to be associated with a strong coupling between subjective craving and smoking (Berkman et al., 2011). Although the neural network underlying inhibitory control and its association with substance dependence have been widely investigated, the pharmacology of inhibitory control is an ongoing scientific endeavor. Animal studies suggest that dopamine plays an important role in overall executive functioning. For example, a hallmark study by Brozoski et al., (1979) indicated that dopamine depletion of the monkey prefrontal cortex impaired spatial working memory. In addition, reduced dopamine D2/D3 receptor availability in rats appeared to be associated with elevated impulsivity levels (Dalley et al., 2007). Based on human studies, theorists assume that the relation between dopamine and cognitive control follows an inverted U-shaped curve such that either too low or too high levels of prefrontal dopamine are disadvantageous for cognitive functioning (Cools and D'Esposito, 2011). The inverted U-curve theory further describes a distinct role for dopamine D1 and D2 receptors. Dopamine D1 receptors are mainly expressed in prefrontal regions and appear to be associated with tonic modulation of prefrontal brain activation which is associated with cognitive stability, while dopamine D2 receptors are most prominent in subcortical regions and appear to be associated with implementing flexible behavior. The proposed association between dopamine and cognitive functioning in the inverted U-curve theory is mainly based on studies investigating working memory performance, but it is likely that other cognitive functions depending on prefrontal

brain activation are similarly characterized by an inverted U-shaped curve. Recent studies in humans have shown that optimal dopamine levels (i.e., extracellular dopamine and receptor densities) exist for attentional capacity (Finke et al., 2010) and also inhibitory control (Nandam et al., 2011), although these studies are still scarce. It is important to gain more knowledge on how dopamine affects neural networks underlying inhibitory control, to better understand disorders such as substance dependence that are characterized by dysfunctional dopamine systems (Balfour, 2009; Berkman et al., 2011; Diekhof et al., 2008; Franken et al., 2005; Koob and Nestler, 1997; Volkow et al., 2009). For example, reduced dopamine D2 receptor densities in the striatum have been consistently found in substance dependent individuals (Martinez et al., 2004; Volkow et al., 2001, 2002; Wang et al., 1997) including smokers (Fehr et al., 2008). These reduced dopamine D2 densities have also been linked to reduced metabolism in prefrontal areas (Volkow et al., 1993, 2001, 2007). Altogether, it is suggested that alterations in dopaminergic functioning in substance dependent individuals may underlie the observed deficits in inhibitory control as well as hypoactivation in associated prefrontal regions. Increased knowledge concerning the role of dopamine in inhibitory control may contribute to a deeper understanding of dopaminergic medications and the limited efficacy of both dopamine agonists and dopamine antagonists in the treatment of addiction until now (Amato et al., 2007; Elkashef et al., 2005).

To the best of our knowledge, only one study employed a dopamine manipulation in substance dependent individuals while measuring inhibitory control (Li et al., 2010). It was shown that the dopamine agonist methylphenidate enhanced inhibitory control compared to placebo in cocaine dependent individuals. The behavioral improvement in inhibitory control was positively associated with activation in the middle frontal gyrus and negatively with activation in the ventromedial prefrontal cortex (Li et al., 2010). Although this study provided valuable insights, a control group consisting of healthy participants was lacking. The aims of the current study were twofold. First, a dopamine manipulation was employed to investigate the role of dopamine in inhibitory control and associated brain activation. Second, the potential link of dopamine with impaired inhibitory control in nicotine dependence was investigated by comparing the effects of dopaminergic manipulation between smokers and non-smoking controls. As part of a larger study (Luijten et al., 2012), participants received placebo and haloperidol in a double-blind randomized cross-over design while performing a Go/NoGo task during fMRI scanning. Haloperidol is a predominant D2/D3 post-synaptic receptor antagonist. As D2 receptors are mainly expressed in subcortical regions (Hall et al., 1994), it can be expected that haloperidol modulates inhibitory control and prefrontal brain functioning via blockade of the indirect basal ganglia pathway in the cortical-thalamic-striatal network

underlying inhibitory control. Furthermore, in line with previous studies showing beneficial effects of a dopamine agonist (Li et al., 2010; Nandam et al., 2011), we hypothesized that haloperidol will reduce inhibitory control and associated brain activation. Second, based on the inverted 'U' curve theory of dopamine and cognitive control, and reported baseline differences between smokers and controls in dopamine D2 receptor density in subcortical regions, we expected that haloperidol will have differential effects on brain activation associated with inhibitory control in smokers and non-smokers.

2. Experimental procedures

2.1. Participants

Twenty-five smokers and twenty-five non-smoking controls participated in this study. Data from two non-smokers were discarded due to technical problems during data acquisition and analysis. The final sample consisted of 25 smokers (mean age=22.56 years, $SD=2.84$, 18 male) and 23 non-smoking controls (mean age=21.74 years, $SD=1.82$, 14 male). Smokers smoked at least 15 cigarettes per day ($M=19.12$, $SD=3.37$; range 15-25) for a duration of at least three years ($M=7.20$, $SD=3.01$, range=3-14). The average score on the Fagerström Test for Nicotine Dependence (FTND: Heatherton et al., 1991; Vink et al., 2005) for smokers was 3.80, $SD=3.37$, range=1-8. Non-smokers had smoked ten cigarettes or less during their lifetime ($M=1.73$, $SD=2.62$, range=0-10). All participants underwent a medical examination by a psychiatrist to assure eligibility for a single dose of 2 mg oral haloperidol. Exclusion criteria for both groups were (a) current substance abuse or dependence (other than nicotine for the smoking group), (b) the current presence of any physical or psychological illness, (c) any use of psychotropic medication or medication that may affect blood circulation and/or respiration, (d) fMRI contraindications, and (e) left-handedness (see supplementary materials for details on medical screening). There were no significant differences between the groups in mean age, $t(46)=1.20$; ns, gender ratio, $\chi^2(1, n=48)=0.67$; ns and education level $\chi^2(2, n=47)=3.19$; ns. The study was conducted in accordance with the Declaration of Helsinki and all procedures were carried out with the adequate understanding and written informed consent of the subjects. The ethics committee of Erasmus MC—University Medical Center Rotterdam approved this study.

2.2. Dopaminergic manipulation

A single oral dose of 2 mg haloperidol and a placebo was administered to participants in a double-blind randomized cross-over design. Haloperidol is a selective dopamine D2/D3 receptor antagonist for postsynaptic receptors. Using positron emission tomography (PET), Nordstrom et al. (1992) demonstrated that striatal D2 receptor occupancy 3 h after oral administration of a single dose of 2 mg haloperidol was 18% and 52% after 6 h. In the present study, the fMRI session took place 4 h after administration which, according to the Nordstrom et al. (1992) study results in about 30% D2 receptor occupancy. Haloperidol has also been found to block dopamine bursts in the prefrontal cortex (Wang and Goldman-Rakic, 2004) and previous studies showed that 2 mg haloperidol successfully reduced processing biases in substance dependent individuals (Franken et al., 2004; Mahler and De Wit, 2005). None of the participants reported any side effects of medication. After study completion (i.e., after the second test occasion) participants were asked to indicate their own belief about the order in which they received the two types of medication (i.e., haloperidol-placebo or placebo-haloperidol). 46.7% correctly indicated the order in which they received the two types of medication types.

As there are only two options (i.e., haloperidol-placebo or placebo-haloperidol) it can be expected that 50% of the participants correctly indicate the order of the two types of medication by chance alone. Using a one-sample t-test we found that 46.7% does not differ significantly from chance level (i.e., 50%), $p=0.7$, suggesting that there were no subjective medication effects that introduced self-unblinding.

2.3. Procedures

After confirmation of study eligibility by the medical screening performed by a psychiatrist, two scanning sessions were scheduled that were separated by one week. Similar to previous studies using haloperidol (Franken et al., 2008,2004), participants took the medication 4 h before both scanning sessions. Smokers were not allowed to smoke after taking the medication until scanning was finished to ensure that indirect nicotine effects on dopamine levels did not interfere with the binding of haloperidol to D2/D3 receptors in the brain. Breath carbon monoxide (CO) concentration was measured in all subjects using a calibrated Micro+Smokerlyzer (Bedfont Scientific Ltd., Rochester, UK) to verify smoking abstinence and to objectively define smokers and non-smokers. In addition, smokers completed the FTND (Heatherton et al., 1991; Vink et al., 2005) to measure nicotine dependence on the first scanning session only and the Questionnaire of Smoking Urges (QSU: Cox et al., 2001) to indicate their current subjective craving for a cigarette during both scanning sessions.

2.4. Task paradigm

Participants completed a Go/NoGo task in which letters were presented at 1 Hz (similar to previous studies such as Nestor et al., 2011). Each letter was presented for 700 ms followed by a blank screen (the interstimulus interval) for 300 ms. Participants were required to make a button press response as fast as possible to each letter (Go trials) and to withhold this response whenever the letter was the same as the previous one (NoGo trials). NoGo trials were presented unpredictably by introducing jitter in the number of intervening Go trials ($M=7.25$, range=3-16). The task consisted of 817 Go and 110 NoGo trials such that twelve percent of all trials were NoGo trials. Four fifteen seconds rest periods were included in the task. Behavioral outcome measures for this task are Go and NoGo accuracy (percentage correct trials) and reaction times for correct Go and incorrect NoGo trials

2.5. Image acquisition

Data were acquired on a 3 T GE Healthcare (The Discovery[®] MRI 750 3.0 T, Milwaukee, US) scanner. Blood oxygen level-dependent (BOLD) sensitive functional T2*-weighted images were acquired in 44 axial slices covering the entire supratentorial brain with a repetition time (TR) of 2500 ms, echo time (TE) of 30 ms, field of view (FOV) of 240 mm, and isotropic voxel size of 2.5 mm³. A structural 3-dimensional (3D) inversion recovery fast spoiled gradient echo T1-weighted image was acquired in 164 contiguous axial slices with TR of 7.9 ms, TE of 3.1 ms, FOV of 240 mm, and isotropic voxel size of 1 mm³ for anatomical reference.

2.6. Image processing

Imaging data were analyzed using SPM8 (Statistical Parametric Mapping; Wellcome Trust Center for Neuroimaging, London, UK). Preprocessing of the functional data included realignment of all functional images. Next, the anatomical scan was coregistered to the mean T2*-weighted image and subsequently segmented into gray and white matter and cerebrospinal fluid. Segmentation parameters were

used for normalization using the SPM T1-weighted MNI template. Functional scans were spatially smoothed using a 3D full-width at half-maximum Gaussian kernel of 4 mm. The four conditions (NoGo correct, NoGo incorrect, Go correct and Go incorrect) were modeled in the context of the general linear model for both types of medication (placebo, haloperidol) using delta functions convolved with a canonical hemodynamic response function. Subsequently, the NoGo correct minus Go correct contrast representing brain activation associated with inhibitory control was calculated for placebo and haloperidol separately.

In order to show that the current Go/NoGo task activated the inhibitory control network the main effect for brain activation associated with inhibitory control was calculated using a single random effects one-sample t-test that included both medication types and both groups.

To investigate the overall effect of haloperidol in all participants on brain activation associated with inhibitory control a main effect of medication (placebo minus haloperidol and vice versa) was calculated by means of a random effects paired-sample t-test of both groups combined. The same analysis was performed for Go trials to investigate whether haloperidol altered baseline activation (see supplementary materials for details).

To assess Group x Medication interactions for brain activation associated with inhibitory control, first an OR map was created according to the methods used in Hester et al. (2009). The OR map shows voxels in which group differences were significant in either of the constituent maps (i.e., brain activation for placebo and haloperidol). Using the OR map, group differences are identified while biases towards either of the medication types are avoided. Second, contrast values (parameter estimates) for both groups and medication types were extracted for significant clusters in the OR map. Subsequently, extracted contrast values were entered in Medication x Group Repeated Measures Analyses of Variance (RM-ANOVA) using SPSS (version 17, Armonk).

In addition, the extracted contrast values from the OR map were correlated with NoGo accuracy for both groups and medication types separately to assess associations between brain activation and behavioral outcome measures. The association between the effects of haloperidol on behavioral measures and brain activation was investigated by calculating Pearson correlation coefficients for placebo minus haloperidol NoGo accuracy scores and placebo minus haloperidol brain activation.

The correction for multiple comparisons in the between medication and the between group analyses (OR map) was performed using a Monte Carlo simulation in imaging space using a dedicated program, Alphasim (a method previously outlined in the literature: Forman et al., 1995; Suckling and Bullmore, 2004; Thirion et al., 2007). One thousand permutations determined that a cluster of 536 mm³ was needed to correct an individual voxel type 1 error of $p < 0.01$ to a cluster corrected threshold of $p < 0.01$. The correction for multiple comparisons for the main effect for task related brain activation was also performed using Alphasim and was corrected to $p < 0.01$ using an individual threshold of 0.0000001 and cluster size restriction of 16 mm³.

2.7. Data analyses questionnaires and behavioral performance

RM-ANOVA's were performed in SPSS for CO levels, QSU scores and behavioral outcomes of the Go/NoGo task. Medication was used as two-level within-subject factor (haloperidol versus placebo) and Group was used as two-level between-subject factor (smokers versus controls) for CO levels and behavioral outcomes. In addition, Task Condition was added as a within-subject factor for behavioral performance (Go versus NoGo correct for accuracy rates and Go versus NoGo incorrect for reaction times).

3. Results

3.1. CO levels and questionnaire data

Smokers had a higher CO breath concentration (in parts per million, $M_{\text{haloperidol}}=6.20$, $SD=3.39$, $M_{\text{placebo}}=6.72$, $SD=3.50$) as compared to non-smoking controls ($M_{\text{haloperidol}}=1.43$, $SD=0.79$, $M_{\text{placebo}}=1.65$, $SD=0.51$), $F(1,46)=52.77$, $p < 0.001$. CO levels did not differ between medication types for either group, $F(1,46)=1.68$, ns. Subjective craving in smokers was equal for placebo ($M=39.71$, $SD=11.48$) and haloperidol ($M=38.08$, $SD=11.80$) conditions $F(1,23)=0.44$, ns.

3.2. Behavioral performance

Accuracy rates revealed a robust main effect of Task Condition (Go versus NoGo), $F(1,46)=458.45$, $p < 0.001$, showing that participants were generally less accurate for NoGo than for Go trials (57.66 versus 97.97%). Furthermore, a main effect of Medication type was found, indicating that accuracy rates were lower during the haloperidol than the placebo condition, $F(1,46)=10.62$, $p < 0.01$. A Medication x Task Condition interaction, $F(1,46)=504.23$, $p < 0.01$, showed that the decrease in performance was driven by the NoGo condition as the effect of medication was significant for the NoGo condition ($M_{\text{NoGo/haloperidol}}=54.02$, $SD=17.22$, $M_{\text{NoGo/placebo}}=61.19$, $SD=14.49$, $F(1,46)=10.91$, $p < 0.01$), and not for the Go condition ($M_{\text{Go/haloperidol}}=97.58$, $SD=3.59$, $M_{\text{Go/placebo}}=98.17$, $SD=3.44$). No main, $F(1,46)=0.28$, ns, or interaction effect, $F(1,46)=0.78$, ns, was found for Group. We performed an additional explorative Group x Condition RM-ANOVA for accuracy rates on the first test occasion in order to exclude possible learning effects on task performance. A Group x Task Condition interaction was found, $F(1,46)=4.72$, $p < 0.05$. Post-hoc t-tests revealed that, for NoGo trials, smokers performed less accurately than non-smoking controls ($p < 0.05$; $M_{\text{smokers}}=53.31$, $SD=14.22$, $M_{\text{controls}}=61.90$, $SD=15.10$), whereas there was no difference for Go accuracy between the groups, $F(1,46)=0.33$, ns.

With regard to the reaction time data, a main effect of Task Condition was found, $F(1,46)=42.03$, $p < 0.001$, indicating that participants generally responded faster for incorrect NoGo trials ($M_{\text{NoGo incorrect/smokers}}=350.77$, $SD=49.31$, $M_{\text{NoGo incorrect/controls}}=313.85$, $SD=41.71$) than for Go trials ($M_{\text{Go/smokers}}=367.51$, $SD=45.81$, $M_{\text{Go/controls}}=337.83$, $SD=40.50$). Furthermore, a main effect was found for Group showing that smokers had generally slower response times, $F(1,45)=7.10$, $p < 0.05$. No main or interaction effects of Medication were found for reaction times (all F 's smaller than 0.82).

3.3. fMRI data

In line with meta-analyses (Garavan et al., 2006; Swick et al., 2011), inhibitory control was associated with brain activation in bilateral IFG, ACC/pre-SMA, DLPFC, anterior insula, temporoparietal junction (TPJ), caudate and putamen, and bilateral superior parietal regions (for an overview of activated brain areas for NoGo minus Go see supplementary Figure 1).

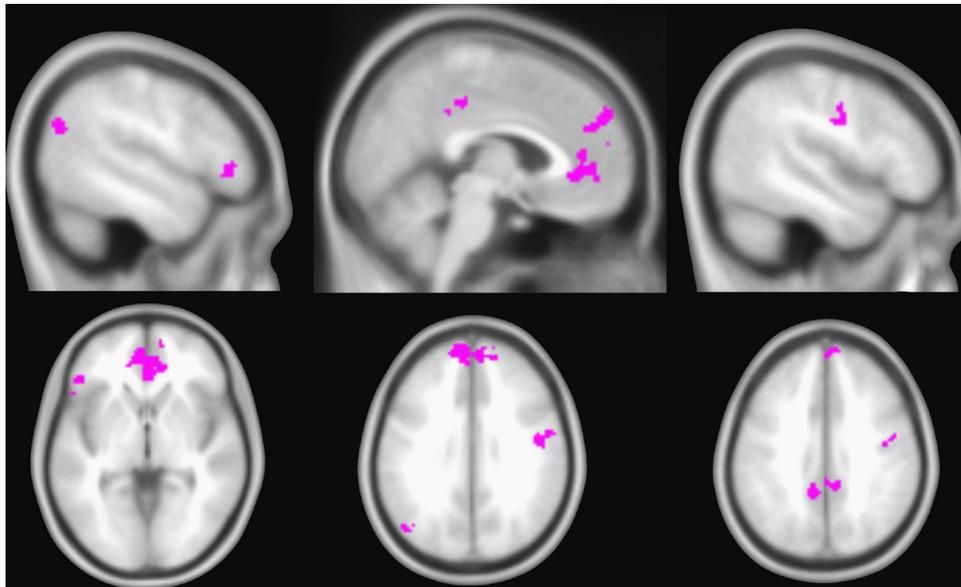


Figure 1 Reduced brain activation associated with inhibitory control after haloperidol across smokers and non-smoking controls. $p < 0.01$ (corrected). See [Table 1](#) for anatomical localization of active regions.

Table 1 Medication effects for brain activation associated with inhibitory control.

Region	MNI coordinates (X Y Z)			mm ³	Z-Value ^a
ACC	-8	52	2	7816	4.12
r-SFG	20	-12	30	744	3.48
l-IFG	-52	34	2	544	3.54
PCC	-8	-46	38	1304	3.44
l-MTG	-50	-70	26	768	3.95

^a $p < 0.01$ (corrected); AAC: anterior cingulate cortex; r-SFG: right superior frontal gyrus; l-IFG: left inferior frontal gyrus; PCC: posterior cingulate cortex; l-MTG: left middle temporal gyrus.

Haloperidol was found to decrease, as compared to placebo, brain activation associated with inhibitory control across groups in the ACC, right superior frontal gyrus (SFG), left IFG, posterior cingulate cortex (PCC), and left middle temporal gyrus (MTG; see [Figure 1](#) and [Table 1](#) for details). There was no increase in brain activation with haloperidol compared with placebo. An additional analysis on the effect of haloperidol on Go-trials confirmed that the reduction in brain activation for inhibitory control was not due to baseline alterations associated with haloperidol (see [supplementary materials](#)). The *OR* map showed differences between smokers and non-smoking controls in the ACC, PCC, right middle frontal gyrus (MFG), left IFG, and right temporoparietal junction (TPJ). Overall, smokers had reduced activation in the ACC relative to controls. Group \times Medication interactions were significant in the right MFG, left IFG, PCC and right TPJ. Post-hoc analyses revealed that activation differences between smokers and non-smoking controls were mainly found after placebo. Activation was reduced in smokers relative to controls after placebo in the right MFG and left IFG and increased in the TPJ. Haloperidol

was found to reduce brain activation associated with inhibitory control in the left IFG and right MFG only in controls, whereas it reduced brain activation in the PCC in smokers. See [Figure 2](#) and [Table 2](#) for details concerning group differences and Group \times Medication interactions.

Correlation analyses of average contrast values extracted from brain activation showing between group differences (ACC, left IFG, right MFG, PCC and right TPJ) with NoGo accuracy ([Figure 3](#)) revealed that activation in the ACC during haloperidol was positively associated with NoGo accuracy $r = 0.43$, $p < 0.05$ in non-smoking controls. The difference in NoGo accuracy between placebo and haloperidol administration in controls was further associated with the difference in brain activation in this area, $r = 0.41$, $p = 0.05$, indicating that a decrease in brain activation after haloperidol administration correlated with a decrease in accuracy. This association between haloperidol-induced differences in brain activation and NoGo accuracy was also found in controls in the right MFG, $r = 0.49$, $p < 0.05$. No significant correlations between brain activation and behavioral measures were found in smokers.

4. Discussion

The aim of the current study was to elucidate the role of dopamine in inhibitory control and associated brain activation. In addition, by comparing smokers and non-smokers the potential link between dopamine and reduced inhibitory control in addiction was investigated. The current results confirmed the hypothesis that reduced dopamine levels after haloperidol intake are associated with impairments in inhibitory control. Haloperidol reduced NoGo accuracy rates in both groups, while Go accuracy and reaction times were unaffected, indicating a specific effect of dopamine on inhibitory control. Impaired inhibitory control after haloperidol was accompanied by reduced activation in prefrontal regions associated with inhibitory control including the ACC,

Table 2 Group differences in brain activation associated with inhibitory control.

Region	MNI coordinates (X Y Z)			mm ³	Z-Value ^a	Group x Medication ^b	Group effects ^b	Medication effects ^b
r-MFG	20	64	12	640	3.59	$F=4.55, p<0.05$	PL: smokers < controls $F=16.30, p<0.001$ HA: ns	HA < PL in controls $F=3.29, p=0.08$
l-IFG	-52	18	16	592	3.27	$F=4.20, p<0.05$	PL: smokers < controls $F=13.71, p=0.001$ HA: ns	HA < PL in controls $F=6.92, p<0.05$
ACC	14	40	8	888	3.66	Ns	Main effect: smokers < control $F=14.60, p<0.001$	Main effect: HA < PL $F=3.37, p=0.07$
r-TPJ	64	-20	30	864	3.57	$F=4.18, p<0.05$	PL: smokers > controls $F=19.67, p<0.001$ HA: ns	HA < PL in smokers $F=2.87, p=0.10$
r-PCC	8	-38	42	672	4.23	$F=5.63, p<0.05$	PL: ns HA: smokers < controls $F=17.33, p<0.001$	HA < PL in smokers $F=14.54, p<0.001$

^aZ-value for group differences in OR map with $p<0.01$ (corrected).

^bDegrees of freedom F -test: 1,46; r-MFG: right middle frontal gyrus; l-IFG: left inferior frontal gyrus; AAC: anterior cingulate gyrus; r-TPJ: right temporoparietal junction; r-PCC: right posterior cingulate cortex; PL: placebo; HA: haloperidol.

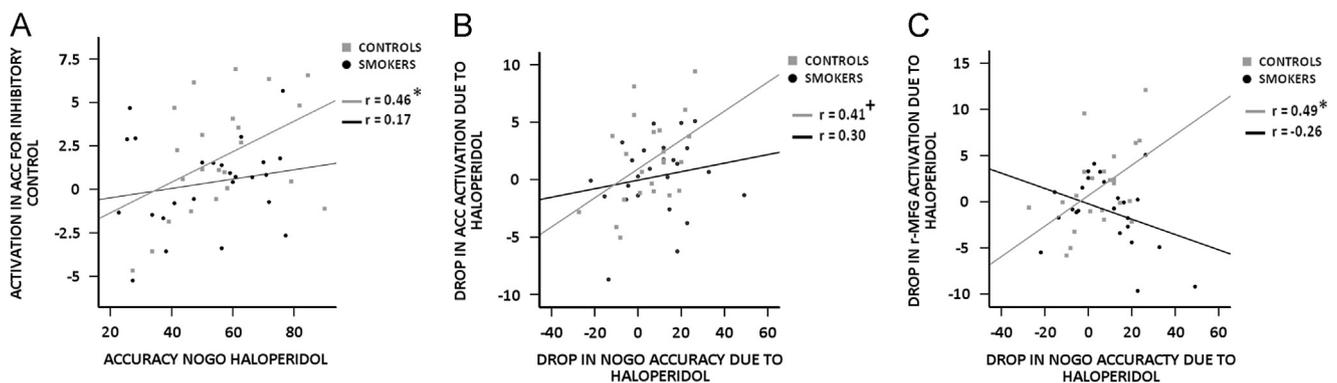


Figure 3 Correlations for NoGo task performance and brain activation associated with inhibitory control $a+p=0.053$, $*p<0.05$; Part A displays the association between NoGo accuracy and brain activation associated with inhibitory control in the anterior cingulate cortex (ACC) during haloperidol. Part B and C displays the association between the drop in NoGo accuracy due to haloperidol (calculated by NoGo accuracy placebo minus NoGo accuracy haloperidol) and the drop in brain activation for inhibitory control in the ACC and the right middle frontal gyrus (r-MFG) due to haloperidol respectively (calculated by brain activation during placebo minus brain activation during haloperidol). The ACC and r-MFG correspond to the brain regions displayed in Figure 2.

activity relative to placebo in prefrontal regions in non-smoking controls, but not in smokers. This implies that dopamine D2/D3 receptor blockade by haloperidol renders non-smoking controls more similar to smokers regarding reduced inhibitory control and hence presumably regarding dopamine levels. The lack of an effect of haloperidol administration on prefrontal brain activation in smokers further implies a relative insensitivity in prefrontal brain regions to dopamine antagonist administration in this group. The findings of the current study are in line with the inverted 'U' shape theory stating that there is an optimum for dopamine levels in the brain to efficiently execute cognitive control (Cools and D'Esposito, 2011). The reduction in inhibitory control after haloperidol in both groups and the larger impact of haloperidol on prefrontal brain activation in non-smoking controls provides indirect

evidence that impairments in inhibitory control in smokers and other addicted population may be due to suboptimal dopamine levels. Therefore it can be concluded that the effects of reduced dopamine D2 receptor densities in smokers in subcortical regions (Fehr et al., 2008), or in substance dependence in general, may not be limited to motivational processes linked to dopamine such as reward sensitivity, but could also be the underlying neurobiological mechanism for reduced inhibitory control. The reduced D2 receptor densities in subcortical regions in addicted individuals may change indirect subcortical-cortical feedback loops in the inhibitory control network, thereby modulating prefrontal brain activation and reducing inhibitory control. It would be interesting for future studies to administer both a dopamine agonist and antagonist in order to examine the full range of the inverted U-curve theory on dopamine levels

and cognitive control and their consequences for nicotine dependence. In addition, future studies may seek to combine fMRI with simultaneous PET imaging to directly assess dopaminergic transmission together with brain activation associated with specific cognitive processes such as inhibitory control (Judenhofer et al., 2008).

It should be noted that inhibitory control and the underlying cortical-striatal-thalamic pathway is not only modulated by dopamine. Evidently, other neurotransmitters such as norepinephrine and acetylcholine also regulate activation in this network and consequently are associated with inhibitory control capacity (Nieuwenhuis and Jepma, 2011; Sarter et al., 2009). Recent work has examined whether improving norepinephrine and dopamine levels by medication such as modafinil may concurrently increase inhibitory control (Brady et al., 2011). Indeed, it has recently been shown that modafinil improved inhibitory control in methamphetamine and alcohol dependent individuals (Dean et al., 2011; Schmaal et al., 2012). In addition, while haloperidol predominantly has its effects on the dopamine system via blockade of D2/D3 receptors, previous studies have also reported modulatory effects of haloperidol on the norepinephrine system (Amato et al., 2011), which is an important consideration for the interpretation of current study results.

In conclusion, an experimental reduction in dopamine levels was associated with impaired inhibitory control and reduced brain activation in smokers and non-smokers. In line with contemporary theories on addiction, smokers showed behavioral deficits on the Go/NoGo task as well as hypoactivity in the left IFG, right MFG and ACC during placebo, thereby confirming previous findings of prefrontal hypoactivation in smokers. Prefrontal brain activation associated with inhibitory control in smokers and non-smokers appears to be differentially affected by the experimental manipulation of dopamine levels, which is in line with the inverted 'U' curve theory of dopamine and cognitive control. The current findings suggest that optimal dopamine levels are crucial to effectively implement inhibitory control. Altered baseline dopamine levels in addicted individuals may contribute to the often observed reduction in inhibitory control in these populations. Based on these findings pharmacotherapy should be targeted at restoring the dopamine balance in smokers, specifically in prefrontal brain regions. The current findings further have implications for other psychiatric and neurological disorders that are also characterized by difficulties in inhibitory control and dopaminergic abnormalities such as attention deficit hyperactivity disorder and Parkinson's disease.

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Contributors

Study designs: IHAF, ML, DJV, RH; data collections: ML, LP (psychiatric screening); data analyses: ML, IMTN, RH, DJV, MS; manuscript writings: ML, IHAF, DJV, RH, MS, IMTN, LP.

Conflicts of interest

The authors have no conflicts of interests regarding the integrity of the reported findings.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.euroneuro.2012.10.017>.

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