

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

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Submitted abstract:

De rol van dopamine in gedragsinhibitie bij rokers en niet-rokers

Een verminderd vermogen tot gedragsinhibitie is karakteristiek voor verslaving inclusief rokers. Het is bekend dat de mate van gedragsinhibitie afhankelijk is van optimale dopamine niveaus en dat rokers minder dopamine receptoren hebben. Hieruit volgt dat een dopamine manipulatie een ander effect zal hebben op rokers dan op niet-rokers. De huidige studie onderzoekt hoe de hersenactiviteit gerelateerd aan inhibitie in rokers en niet-rokers wordt beïnvloed door dopamine.

Taak prestatie en hersenactiviteit werd twee maal gemeten in 25 rokers en 23 niet-rokers door middel van fMRI terwijl deelnemers een GO-NOGO taak uitvoerden.

Haloperidol (2mg), een selectieve D2/D3 dopamine remmer, of placebo werd 4 uur van tevoren ingenomen middels een dubbelblind gerandomiseerd cross-over design.

Haloperidol verlaagde de mate van gedragsinhibitie. Dit was gerelateerd aan een verlaging van de hersenactiviteit in frontale en pariëtale hersendelen. Rokers hadden verminderde activiteit gerelateerd aan gedragsinhibitie in prefrontale gebieden na placebo. Dit is in overeenstemming met huidige theorieën die verminderde gedragsinhibitie verklaren. Na haloperidol was de hersenactiviteit in prefrontale gebieden gelijk tussen rokers en controles. Dit kwam door een afname van activiteit in de controles.

Deze studie bevestigt de belangrijke link tussen dopamine niveaus en gedragsinhibitie. Verder suggereren deze bevindingen dat voornamelijk niet-rokers een verlaging van activiteit laten zien na haloperidol. Dit suggereert dat rokers minder gevoelig zijn voor de dopamine manipulatie, wellicht doordat ze een algemeen laag dopamine niveau hebben. Hieruit kan worden geconcludeerd dat lage dopamine niveaus een onderliggend neurobiologisch mechanisme kan zijn voor een verminderd vermogen tot gedragsinhibitie.

1. Introduction

The ability to guide our behavior according to our long term goals requires the inhibition of automatic behavior. Inhibitory control in healthy individuals is associated with a mainly right lateralized network including the inferior frontal gyrus (IFG), the anterior cingulate gyrus (ACC)/ pre-supplementary motor area (pre-SMA) and dorsolateral prefrontal cortex (DLPFC), as well as parietal and subcortical areas including the thalamus and basal ganglia (Chambers, Garavan, & Bellgrove, 2009; Garavan, Hester, Murphy, Fassbender, & Kelly, 2006; Swick, Ashley, & Turken, 2011). Optimal activation in this neural network may be of great importance when habitual and rigid behavioral patterns should be changed, such as when substance dependent individuals try to control or withhold using a substance of abuse. Several contemporary theoretical models of substance dependence (Goldstein & Volkow, 2002; Jentsch & Taylor, 1999; Lubman, Yucel, & Pantelis, 2004) suggest that neural deficits in the network underlying inhibitory control play an important role in the development and continuation of substance dependence. Indeed, hypoactivation in frontal brain regions associated with inhibitory control has been found in cocaine dependent individuals (Hester & Garavan, 2004; Kaufman, Ross, Stein, & Garavan, 2003), alcohol dependent individuals (Kamarajan et al., 2005) and in smokers (de Ruiter, Oosterlaan, Veltman, van den Brink, & Goudriaan, In Press; Luijten, Littel, & Franken, 2011; Nestor, McCabe, Jones, Clancy, & Garavan, 2011). Reduced inhibitory control has also been found in other impulsive populations such as in children with attention deficit hyperactivity disorder (Groman, James, & Jentsch, 2009) and violent offenders (Chen, Tien, Juan, Tzeng, & Hung, 2005)

The neurotransmitter dopamine is known to play an important role in various aspects of substance dependence. The reinforcing effects of drugs of abuse are depending on dopaminergic firing in the striatum (Balfour, 2009; Koob & Nestler, 1997) and motivational processes in addiction such as subjective craving and reward sensitivity are known to be modulated by dopamine levels (Diekhof, Falkai, & Gruber, 2008; Franken, Booij, & van den Brink, 2005; Volkow, Fowler, Wang, Baler, & Telang, 2009). These behavioral disturbances linked to dopaminergic dysfunction may be associated with reduced dopamine D2 receptor density in the striatum that has been shown repeatedly in substance dependent individuals (Martinez et al., 2004; Volkow et al., 2001; Volkow et al., 2002; Wang et al., 1997) including smokers (Fehr et al., 2008) by using Positron Emission Tomography (PET). Reduced D2 receptor density in cocaine dependent individuals has also been found to be associated with reduced metabolism in prefrontal areas (Volkow et al., 1993), suggesting that the disturbances in dopaminergic functioning in substance dependent individuals may also impact brain functions depending on prefrontal regions such as inhibitory control. Indeed, dopamine has been found to have an important role in cognitive control in

healthy controls. For example, prefrontal dopamine seems to support the active maintenance of goal representations (Brozoski, Brown, Rosvold, & Goldman, 1979) which is a critical function for the active suppression of irrelevant behaviors. 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 seem disadvantageous (Cools & D'Esposito, 2011). However, in contrast to the well-know role of dopamine in disturbed reward and motivational processes in substance dependence (Blum et al., 2000; Franken et al., 2005; Robinson & Berridge, 2008), a gap in the literature exist for the potential role of dopamine in reduced cognitive control in substance dependence individuals. According to the best of our knowledge, only one study investigated the role of dopamine in inhibitory control in substance dependence individuals. This study confirmed a role for dopamine in inhibitory control in cocaine dependent individuals as it was found that the dopamine agonist methylphenidate improved behavioral measures of inhibitory control which was associated with activation in the ventromedial prefrontal cortex (Li et al., 2010). The current study aimed to acquire more information concerning the role of dopamine in inhibitory control and the potential link of dopamine with impaired inhibitory control in smokers. Participants received placebo and haloperidol, a dopamine D2/D3 receptor antagonist, in a double-blind randomized cross-over design while performing a Go-NoGo task during fMRI scanning. We hypothesize that smokers will show reduced inhibitory control and hypoactivation in the network underlying inhibitory control during placebo. Based on the inverted 'U' curve theory of dopamine and cognitive control and the differences between smokers and controls in dopamine D2 receptor density, we expect that the dopaminergic manipulation with haloperidol will have differential effects on brain activation associated with inhibitory control in smokers and non-smokers.

2. Materials and methods

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). 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 influences blood circulation and respiration, (d) fMRI contraindications, and (e) left

handedness. There were no significant differences between the groups in mean age, $t(46) = 1.20$; ns, or gender ratio, $\chi^2(1, n = 48) = 0.67$; ns. 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, Kozlowski, Frecker, & Fagerstrom, 1991; Vink, Willemsen, Beem, & Boomsma, 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). 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 Medical Centre 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 and is known to affect both striatal and prefrontal regions (Nordstrom, Farde, & Halldin, 1992; Y. Wang & Goldman-Rakic, 2004). Nordstrom et al. (1992) demonstrated that D2 receptor occupancy three hours after oral administration of a single dose of 2mg haloperidol was 18% and 52% after six hours. In the present study, testing took place four hours after admission, which, according to the Nordstrom (1992) study would result in about 30% D2 receptor occupancy. Previous studies showed that this dose of haloperidol influenced cognitive performance (Franken, Hendriks, Stam, & Van den Brink, 2004; Mahler & de Wit, 2005). None of the participants reported any side effects of medication and were reported by participants guess' on type of medication they received for each scanning sessions were not above chance (46.7% of the participants correctly indicated on which test occasion they received haloperidol).

2.2. 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. Participants took the medication four hours 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 transmission did not interfere with the binding of haloperidol on D2/D3 receptors in the brain. Breath carbon monoxide concentration was measured in all subjects using a calibrated Micro+Smokerlyzer (Bedfont Scientific Ltd., Rochester, UK) to objectively define smokers and nonsmokers. 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 for both scanning sessions.

2.4 Task paradigm

Participants completed a Go/NoGo task in which vowels were presented at 1 HZ. Each stimulus was presented for 700 ms and a blank screen (the interstimulus interval) for 300 ms. Participants were required to make a button press response as fast as possible to each vowel (Go trials) and to withhold this response whenever a vowel was the same as the previous one (NoGo trials). NoGo trials were presented unpredictably by introducing jitter in the number of intermitted Go trials ($M = 7.25$, range 3-16). Twelve percent of all trials were NoGo trials resulting in a total number of 110 NoGo trials.

2.5 Data analysis and image acquisition

Group x medication Repeated Measures Analyses of Variance (RM-ANOVA; with Greenhouse-Geisser adjusted p-values when necessary) were applied to analyze CO levels, and behavioral outcomes of performance on the Go-NoGo task. The between subject factor Group was omitted for QSU craving scores. Task condition was added as a within subjects factor to investigate behavioral components of inhibitory control (Go versus NoGo correct for accuracy rates and Go versus NoGo incorrect for reaction times). A Bonferroni correction for multiple comparisons was applied in all post-hoc analyses.

Blood oxygen level-dependent (BOLD) fMRI data were acquired on a 3-T General Electric Healthcare (The Signa® MRI 750 3.0T) scanner. 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 2.5x2.5x2.5 mm. A structural 3-dimensional T1-weighted image was acquired in 164 1 mm axial slices with TR of 7.9 ms, TE of 3.1 ms, FOV of 240 mm, and isotropic voxel size of 1x1x1 mm. Imaging data were analyzed using SPM8 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, 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. Segmentation parameters were used for normalization using a SPM T1 MNI template. Functional scans were spatially smoothed using a full-width at half-maximum Gaussian kernel of 4 mm. Four conditions, namely NOGO correct, NOGO incorrect, GO correct and GO incorrect were modeled in the context of the general linear model for both medication conditions, using delta functions convolved with a canonical hemodynamic response function. To investigate brain activation related to inhibitory control a contrast was calculated

for NoGo versus Go trials only including the correct trials in both conditions for each medication conditions separately. Main effects for brain activation related to inhibitory control was calculated in a second-level random effects analyses across medication condition and groups using a one-sample t-test and corrected for multiple comparisons using $p < .05$ family wise error correction. The main effect of medication across groups was calculated by mean of a paired-sample t-test across groups. An independent samples t-test was used to test for differences between groups by means of OR maps for both medication conditions. An OR map includes the voxels in which group differences appear significant from either of the constituent maps, thereby avoiding biases to either of the medication conditions. To correct for multiple comparisons in between medication and between group analyses, a Monte Carlo simulation was used to determine the cluster extent necessary. Thousand permutations determined that a cluster of 536mm³ was needed to correct an individual voxel type 1 error of $p < .01$ to a cluster corrected threshold of $p < .01$. For clusters showing between group differences in the OR map, group by condition interactions were determined through follow-up RM-ANOVA on extracted beta values using SPSS. In addition, beta values in these regions were correlated with NoGo accuracy scores for both groups and medication conditions separately, as well as correlations for the change in brain activation due to haloperidol intake and the change in behavioral performance due to haloperidol intake (i.e. correlations were calculated for placebo minus haloperidol NoGo accuracy scores and placebo minus haloperidol brain activation).

3. Results

3.1 CO levels, questionnaire data and behavioral performance

Smokers had a higher breath concentration of carbon monoxide (CO; 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 conditions. Subjective craving in smokers was equal for placebo ($M = 39.71$, $SD = 11.48$) and haloperidol ($M = 38.08$, $SD = 11.80$) sessions $F(1,23) = 0.44$, ns.

The accuracy rates for both the smoking and non-smoking on the Go/NoGo task are displayed in Figure 2 for both medication conditions. A robust main effect for task condition (Go versus NoGo) was found, $F(1,46) = 458.45$, $p < .001$, showing that participants were less accurate on NoGo than on Go trials (97.87% versus 57.66%). Furthermore, a main effect for medication type was found, indicating that accuracy rates are lower during haloperidol than during placebo, $F(1,46) = 10.62$ $p < 0.01$. A Medication x Task Condition interaction, $F(1,46) = 504.23$ $p < .01$, showed that the decrease in performance was

driven by the NoGo condition as the effect for medication was significant in the NoGo condition ($M_{\text{NoGo}/\text{haloperidol}} = 54.02$, $SD = 17.22$, $M_{\text{NoGo}/\text{placebo}} = 61.19$, $SD = 14.49$, $F(1,46) = 10.91$, $p < 0.01$), and not in the Go condition ($M_{\text{Go}/\text{haloperidol}} = 97.58$, $SD = 3.59$, $M_{\text{Go}/\text{placebo}} = 98.17$, $SD = 3.44$). Smokers and non-smoking controls showed comparable accuracy rates, as no main or interaction effect was found for Group. We performed an explorative Group x Condition RM-ANOVA for task performance during placebo in those participants who received placebo on the first occasion in order to exclude possible learning effects on task performance. A group x condition interaction was found $F(1,22) = 8.18$, $p < 0.01$. Post-hoc t-tests revealed that, on NoGo trials, smokers performed less accurate than non-smoking controls ($p < 0.01$; $M_{\text{smokers}} = 56.67$, $SD = 12.26$, $M_{\text{controls}} = 69.17$, $SD = 8.15$), whereas there was no difference on accuracy between the groups for Go trials.

With regard to the reaction time data, a main effect for condition was found, $F(1,46) = 42.03$, $p < .001$ indicating that participants generally responded faster to incorrect NOGO trials ($M_{\text{NoGo incorrect}/\text{smokers}} = 350.77$, $SD = 49.31$, $M_{\text{NoGo incorrect}/\text{controls}} = 313.85$, $SD = 41.71$) than to Go trials ($M_{\text{Go}/\text{smokers}} = 367.51$, $SD = 45.81$, $M_{\text{Go}/\text{controls}} = 337.83$, $SD = 40.50$). Furthermore, a main effect was found for group showing that smokers have generally slower response times, $F(1,45) = 7.10$ $p < 0.05$. No effects of medication were found on reaction times.

3.3 fMRI data

Inhibitory control was associated with robust brain activation in bilateral IFG, ACC, DLPFC, anterior insula, temporalparietal junction (TPJ), caudate and putamen and left superior parietal regions (see figure 1).

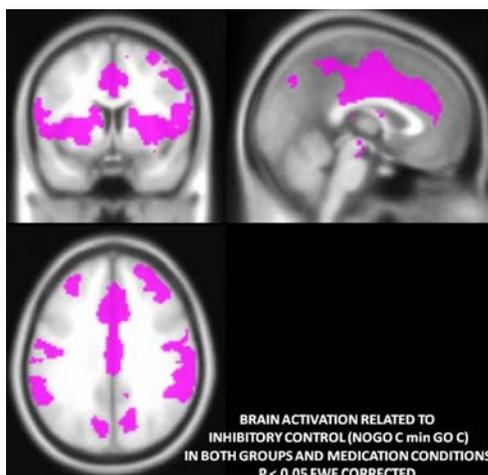


Figure 1 Brain activation for inhibitory control

Haloperidol was found to decrease brain activity related to inhibitory control across groups in the ACC/medial frontal gyrus, posterior cingulate cortex (PCC), left IFG/orbitofrontal cortex (OFC), right pre/post central gyrus and left middle temporal gyrus (see figure 2). No brain regions showed more activation for haloperidol than placebo.

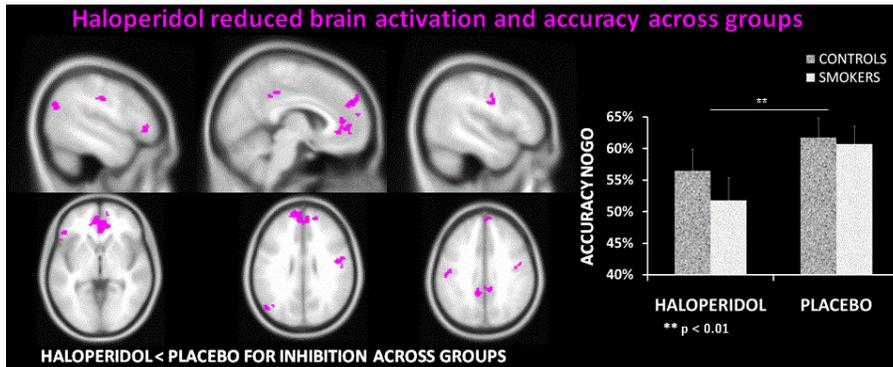


Figure 2 Effect of haloperidol in brain activation and accuracy

The OR map showed differences between smokers and non-smoking controls in the ACC and PCC, right middle frontal gyrus (MFG), left IFG, and right temporalparietal junction. See table 1 and figure 2 for directions of group differences and group x medication interactions.

Table 1 Group differences in brain activation

Region	MNI coordinates (X Y Z)	Group x Medication ^a	Group effects ^a	Medication effects ^a
r-MFG	20 64 12	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	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
vACC	14 40 8	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	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 -32 40	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

^adegrees of freedom F-test: 1,26; r-: right; l-: left; PL: placebo; HA: haloperidol

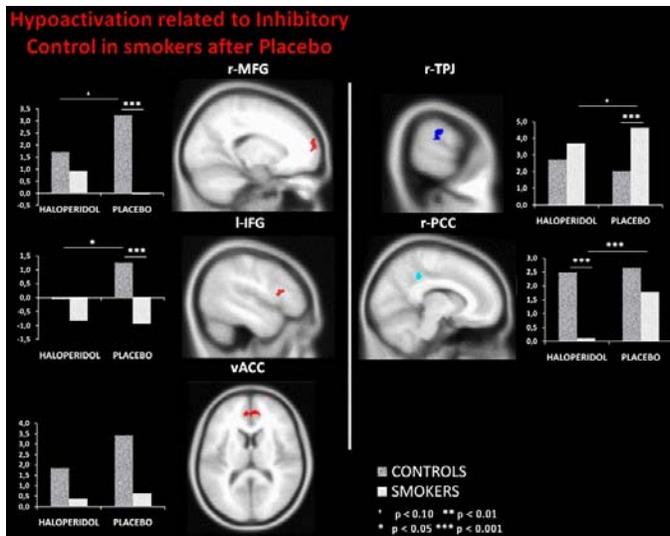


Figure 3 Group differences in brain activation

Brain behavior correlations showed that activation in de ACC during haloperidol was positively associated with accuracy rates for NoGo trials $r = 0.43$, $p < 0.05$ in controls. The difference in accuracy rates between placebo and haloperidol administration in controls was further associated with the difference in brain activation in this area, $r = 0.41$, $p = 0.053$, such that the higher the decrease in brain activation due to haloperidol administration the higher the decrease in accuracy. This association between haloperidol induced differences between accuracy and brain activation was also found in controls in the right middle frontal gyrus, $r = .49$, $p < 0.05$. No significant correlations between behavioral and brain activation measures were found in smokers.

4. Discussion

Consistent with the notion that reduced inhibitory control in smokers is due to improper functioning of the prefrontal cortex, reduced activation associated with inhibitory control in smokers was found in the left IFG, ACC and right MFG after placebo which replicates findings in previous studies (de Ruiter et al., In Press; Nestor et al., 2011). Activation of the right TPJ was enhanced in smokers after placebo suggesting compensational activation of this brain region known to be involved in attention processing (Corbetta & Shulman, 2002). No differences between smokers and controls were found in these regions after haloperidol intake, which could suggest that the administration of a dopamine antagonist is able to normalize brain activation in smokers during an inhibitory control task. However, several findings in the current study argue against this notion. First, haloperidol was found to generally decrease brain activation associated with inhibitory control in the ACC, IFG and MFG as well as to impair behavioral accuracy. The relation between reduced brain activation and impaired behavioral performance was

supported by correlations in non-smoking controls showing an association for the decrease in brain activation after haloperidol and the decreased in behavioral performance. These findings are in line with the notion that low levels of dopamine are disadvantageous for cognitive control. As far as we know, the current study is the first one to demonstrate the link between dopamine levels and brain activation associated with inhibitory control since most studies investigated the role of dopamine in cognitive control by using working memory and mental flexibility paradigms (Bertolino et al., 2010; Braskie et al., 2011; Stelzel, Basten, Montag, Reuter, & Fiebach, 2010). In addition, non-smoking controls seem more sensitive to the reduction in brain activation in prefrontal brain regions after haloperidol intake. Activation patterns in the IFG and MFG show that the reduction in activation in non-smoking controls due to haloperidol intake is responsible for comparable activation patterns for smokers and non-smoking controls after haloperidol. This implies that dopamine D2/D3 receptor blockade by haloperidol may render non-smoking controls more similar to smokers regarding dopaminergic transmission as well as a relative insensitivity to administration of a dopamine antagonist in smokers. The inverted 'U' shape theory stating that there is an optimum for dopamine levels in the brain to efficiently execute cognitive control (Cools & D'Esposito, 2011) may explain these findings. Reduced dopamine D2 receptor density in smokers (Fehr et al., 2008) may cause suboptimal baseline dopamine levels such that smokers are not on top of the inverted 'U' curve, explaining the impairments' in inhibitory control in smokers and reduced brain activation associated with inhibitory control in the ACC, IFG and MFG after placebo. Because of suboptimal baseline dopamine level smokers due to reduced dopamine D2 receptor densities, smokers were less sensitive to the administration of a dopamine antagonist than non-smoking controls. Together, these findings confirm our primary hypothesis that administration of a dopamine antagonist will affect smoker and non-smokers in a different way. Altogether, these findings suggest that the effects of reduced dopamine receptors densities in smokers, 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. It would be interesting for future studies to administer both a dopamine agonist and antagonist in order to compare the differential effects of respectively enhancing and reducing dopaminergic transmission in smokers and non-smoking controls.

It should be noted that results of the current study do not allow drawing conclusions on causality due to the cross-sectional selection of participants. Longitudinal population based neuroimaging studies should be performed in order to test whether alterations in the dopamine system

and the link with reduced inhibitory control are pre-existing for the development of nicotine dependence, are a consequence of repeated smoking, or both.

To summarize, the current study investigated the role of dopamine on brain activation associated with inhibitory control in smokers and non-smoking by administration of the dopamine D2/D3 receptor antagonist. Inhibitory control was impaired in both groups after haloperidol administration due to a reduction in prefrontal brain activation. After placebo, smokers showed hypoactivity in the left IFG, right MFG and ACC associated with inhibitory control, while brain activation in smokers and non-smokers was more similar after haloperidol. Brain activation in non-smokers seemed to be more sensitive to the reduction in dopamine transmission 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 transmission levels in addiction individuals may contribute to the often observed reduction in inhibitory control in these populations. These findings may eventually contribute to the continued search for pharmacotherapy for the treatment for smoking cessation.

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