Putamen functional connectivity during inhibitory control in smokers and non-smokers

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ABSTRACT

The putamen has been shown to play a key role in inhibitory control and addiction, and consists of distinct subregions associated with distinct functions. The anterior putamen is thought to be specialized in goal-directed control or response-monitoring in connection with frontal regions, whereas the posterior part is specialized in habitual or automatic responding in connection with sensorimotor regions. The present study is the first to delineate functional networks of the anterior and posterior putamen in a Go–NoGo response inhibition task, and to examine differences between smokers ($n = 25$) and non-smokers ($n = 23$) within these networks. Functional connectivity analyses were conducted on fMRI data from a Go–NoGo study, using the generalized form of psychophysiological interaction with anterior and posterior putamen seed regions. In the context of inhibition, the anterior putamen exhibited connectivity with the anterior cingulate cortex (ACC) and precuneus ($p_{FWE} < .05$), which was in line with previous literature. Conversely, the posterior putamen showed connectivity with regions implicated in sensorimotor processing. When we compared smokers to non-smokers, we did not observe the expected weaker connectivity between the anterior putamen and ACC during inhibition in smokers. Instead, our study revealed stronger inhibition-related connectivity between the anterior putamen and right insula in smokers. This finding highlights the involvement of putamen – insula interactions in addiction and impulse control.

Keywords functional connectivity, inhibition, insula, putamen, smoking.

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INTRODUCTION

Many smokers continue smoking despite their awareness of negative consequences, and quit attempts often fail (Borland *et al.* 2012). These problems have been linked to deficits in inhibitory control, as smokers often show impaired performance on response inhibition tasks (Smith *et al.* 2014). Examples of such tasks are the 'Stop Signal' and 'Go–NoGo' tasks, where participants attempt

to inhibit their automatic motor response to certain stimuli (Dalley, Everitt & Robbins 2011). Several functional magnetic resonance imaging (fMRI) studies have investigated brain activity during response inhibition in smokers, and smoking was found to be associated with hypoactivation in frontal regions such as the anterior cingulate cortex (ACC), orbitofrontal cortex, and inferior, middle and superior frontal gyri (Luijten *et al.* 2014).

These frontal regions do not operate in isolation, but are considered nodes of a putative response inhibition network also comprising cortical motor areas and basal ganglia structures, in particular the dorsal striatum consisting of putamen and caudate nuclei (Everitt & Robbins 2016; Hampshire & Sharp 2015). Recently, awareness has risen that the investigation of connectivity or synchronization between nodes of brain networks can

provide more information about adaptive and maladaptive processes (Ernst *et al.* 2015). Indeed, connectivity between putamen and frontal cortex appears to be central to successful response inhibition as measured with the Stop Signal task (Zandbelt & Vink 2010), and altered patterns of connectivity between these areas during stop signal inhibition have been found in different types of addictions (Courtney, Ghahremani & Ray 2012; Li *et al.* 2014). This suggests that knowledge of putamen connectivity patterns during response inhibition can contribute to our understanding of inhibitory control deficits in smokers.

Support for the role of the putamen in addiction not only comes from human imaging studies, but also from a substantial body of work in animals (Everitt & Robbins 2016). Within the putamen, a shift in locus of control occurs during the development of an addiction, which in humans seems to take place along an anterior–posterior axis (Sjoerds *et al.* 2013). There is converging evidence for this anterior/posterior distinction within the putamen, where the anterior putamen displays connectivity with frontal areas such as the medial frontal gyrus and ACC, whereas the posterior putamen is connected with sensorimotor areas (Di Martino *et al.* 2008; Draganski *et al.* 2008; Haber 2003; Lehéricy *et al.* 2004). The anterior network is thought to be involved in goal-directed control, whereas the posterior network has been implicated in habitual, over learned responding (Balleine & O'Doherty 2010; de Wit *et al.* 2012; Wu, Chan & Hallett 2008). Recent studies have linked individual differences in the balance between goal-directed and habitual responding to compulsive and addictive behaviours (Gillan *et al.* 2016). This suggests it would be promising to explore the contributions of these systems in smokers.

So far, studies using response inhibition paradigms, such as the Go–NoGo task, have not attempted to delineate anterior (goal-directed) and posterior (habitual) putamen networks during response inhibition, nor have they directly investigated putamen connectivity in relation to smoking.

Therefore, the first aim of our study is to examine functional networks of the anterior and posterior putamen involved in Go-NoGo task performance. We hypothesize that during response inhibition, which requires a habitual response to be overwritten by a goal-directed one, the anterior putamen will show a pattern of functional connectivity with frontal regions involved in response inhibition, such as the ACC. In contrast, given the main role of the posterior putamen in habitual as opposed to goal-directed responding, we expect more functional connectivity between the posterior putamen and sensorimotor areas during repetitive 'Go' responding.

Our second aim is to compare smokers to non-smokers on functional connectivity of the anterior versus posterior putamen during response inhibition. We expect that smokers will exhibit lower functional connectivity between the anterior putamen and frontal areas such as the ACC, reflecting a relatively weak goal-directed control network. Additionally, smokers may show stronger connectivity between the posterior putamen and sensorimotor areas during inhibition, reflecting more interference of the habit network during this condition in comparison to non-smokers.

MATERIALS AND METHODS

Participants

The sample consists of 25 smokers and 23 non-smokers, for which the neural activity during inhibition has been described previously as part of a larger pharmacological fMRI study (Luijten *et al.* 2013). We only used the placebo session of this study. Characteristics of this sample are displayed in Table 1. Smokers consumed a minimum of 15 cigarettes per day ($M = 19.12$, $SD = 3.37$, range = 15–25), for at least three years ($M = 7.20$, $SD = 3.01$, range = 3–14). Smokers had a mean score of 3.80 ($SD = 1.83$, range = 1–8) on the Fagerström Test for Nicotine Dependence (FTND; Heatherton *et al.* 1991). Non-smokers had not smoked

Table 1 *Participant characteristics.*

	Smokers	*Non-smokers*	*Difference smokers versus non-smokers*[a]
N	25	23	n/a
Male	18	14	$\chi^2(1, N = 48) = 0.67$, $p = .414$
Age in years $M(SD)$	22.56 (2.84)	21.74 (1.82)	$t(41.15) = 1.20$, $p = .236$[b]
Education level	84% high, 8% middle, 8% low ($n = 25$)	95.5% high, 4.5% middle, 0% low ($n = 22$)	n/a[c]

[a]To test for significance differences an independent samples *t*-test or chi-square test was used. [b]Given a violation of Levene's test for homogeneity of variances, $F(1, 46) = 6.25$, $p = .016$, a *t*-test not assuming homogeneity of variances was performed. [c]Education level was categorized as low, middle or high according to the Dutch education system. A chi-square test for education level could not be performed because the low and middle categories did not contain sufficient participants. Note: characteristics of this sample have been reported in a previous study (Luijten *et al.* 2013).

more than 10 cigarettes during their lifetime ($M = 1.73$, $SD = 2.62$, range = 0–10). Details on exclusion criteria and testing procedures can be found in the supplement. This study was approved by the ethics committee of Erasmus MC—University Medical Center Rotterdam and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent before participating in this study.

Questionnaires

Smokers completed the FTND (Heatherton *et al.* 1991), which is a measure of nicotine dependence. Before the scanning session, they also completed the Questionnaire of Smoking Urges (QSU; Sanderson Cox, Tiffany & Christen 2001) to report their subjective craving for a cigarette at that time. Additionally, the Barratt Impulsiveness Scale was obtained from all participants as a measure of trait impulsivity (BIS-11; Patton, Stanford & Barratt 1995).

Task paradigm

In this Go–NoGo task (previously described by Luijten *et al.* 2013), participants were required to press a button in response to letters presented for 700 ms at 1 HZ. Between each letter, a blank screen was presented for 300 ms, constituting the inter-stimulus interval. When the same letter was presented consecutively, participants had to withhold their response (NoGo trial). The task consisted of 817 Go trials and 110 NoGo trials. Unpredictability of NoGo trials was established by introducing jitter in the number of Go trials presented in succession ($M = 7.25$, range = 3–16). Four rest periods of 15 seconds were also included in the task. The measures obtained from this task were: accuracy for Go and NoGo trials, and reaction times (RTs) for incorrect NoGo and correct Go trials.

Image processing

For details on image acquisition parameters we refer to the supplement. Analyses were performed using SPM8 (Statistical Parametric Mapping; Wellcome Trust Center for Neuroimaging, London, UK). Pre-processing started with realignment of all functional scans and coregistration of the anatomical scan to the mean T2*-weighted image. Next, the anatomical scan was segmented into grey and white matter and cerebrospinal fluid, and the resulting segmentation parameters were used for normalization to the SPM T1-weighted MNI template. After normalization, the voxel size was $2 \times 2 \times 2$ mm. For spatial smoothing of functional images, we used a Gaussian kernel of 8 mm full width at half maximum. A general linear model (GLM) was created that included the four conditions (Go correct, Go incorrect, NoGo correct and NoGo incorrect), which were modelled using delta functions convolved with a canonical haemodynamic response function (HRF).

Seed regions

In order to create subject specific anatomical seed regions of the putamen, each participant's normalized anatomical image was entered in an automized toolbox for subcortical segmentation in FSL FIRST (Patenaude *et al.* 2011). A line through the anterior commissure was used as a reference point to define the anterior and posterior parts of the putamen. A gap of 4 mm (MNI, $y = -2$ to 2) was left between the two regions to minimize signal overlap.

Functional connectivity

Functional connectivity analyses were performed using the generalized form of psychophysiological interaction (gPPI) toolbox (McLaren *et al.* 2012), which incorporates all task conditions (NoGo correct, NoGo incorrect, Go correct, Go incorrect) in one PPI model. The normalized and smoothed functional images, specified by the original GLM, were used as input for the gPPI toolbox. For each seed region and each participant, a gPPI GLM was created. The gPPI GLM consisted of a physiological regressor, reflecting the physiological activity of the seed region, four psychological regressors, reflecting each of the task conditions, and four PPI regressors, reflecting the psycho-physiological interaction terms. To create the physiological regressor, the first eigenvariate of the timeseries was extracted from the respective seed region. This regressor was subsequently deconvolved to estimate the neuronal activity underlying the observed blood oxygen level dependent (BOLD) signal. Next, the estimated neuronal activity was multiplied with the condition ON times (onset times plus stimulus duration) for each task condition and then convolved with the HRF to form the four PPI regressors. The four psychological regressors were created by convolving the ON times for each condition with the canonical HRF. Finally, a whole-brain analysis (single-subject level) was performed with the gPPI GLM in SPM8. For each seed region and participant, a PPI-contrast was made, contrasting the PPI during the NoGo correct condition (inhibition) with the PPI during the Go correct condition (repetitive responding). The NoGo correct > Go correct contrast is most commonly used to study inhibition (Luijten *et al.* 2014) and corresponds to that used in the previous paper (Luijten *et al.* 2013). The Go correct > NoGo correct side of this contrast, here referred to as 'repetitive responding', is thought to reflect prepotent motor responses which we

Table 2 Functional connectivity across all participants.

Main areas (# voxels)[a]	Side[b]	Total # voxels[c]	p-value cluster[d]	Brodmann areas[e]	Peak voxel (MNI)			t-value peak
					X	Y	Z	
Anterior putamen		*NoGo correct > Go correct*						
Medial superior frontal gyrus (795)	R/L	2252	<.001	10, 32, 24, 11, 25	6	46	0	6.38
Anterior cingulate (626)	R/L							
Medial orbitofrontal cortex (527)	R/L							
Precuneus (171)	R/L	353	.006	31, 7	16	−54	32	4.28
Mid-cingulate (47)	R							
Posterior cingulate (41)	R							
Posterior putamen		*NoGo correct > Go correct*						
Mid-cingulate (723)	R/L	1461	<.001	31, 5, 6, 23, 7, 24, 3, 4	−16	−34	46	5.53
Supplementary motor area (110)	L							
Paracentral lobule (109)	L							
Precuneus (423)	R	1292	<.001	7, 31, 30, 19, 18, 23, 29	20	−54	26	5.53
Cuneus (320)	R							
Calcarine gyrus (256)	R							
Precentral gyrus (89)	R	223	.026	6, 9	44	−4	30	5.05
Postcentral gyrus (38)	R							
Cuneus (387)	L	656	<.001	18, 31, 19, 7	−16	−76	24	4.89
Superior occipital gyrus (117)	L							
Calcarine gyrus (21)	L							
Inferior occipital gyrus (120)	L	298	.008	18, 19, 17	−28	−96	−8	4.68
Lingual gyrus (90)	L							
Middle occipital gyrus (33)	L							

[a]Automatic anatomical localization of clusters was performed using AAL labelling in the WFUpickatlas toolbox. The three largest areas included in a cluster are listed, with # voxels indicating the number of voxels in these areas. [b]Side refers to hemisphere (right/left). [c]# voxels refers to the total number of voxels in a cluster. [d]All results are reported at a cluster-level $p \leq .05$, FWE (familywise error) corrected for multiple comparisons across the whole brain, combined with a voxel-level threshold of uncorrected $p < .001$. [e]Brodmann areas are listed in descending order based on size and labelling of these areas was performed with WFUpickatlas. Note: The comparison Go correct > NoGo correct yielded no significant results.
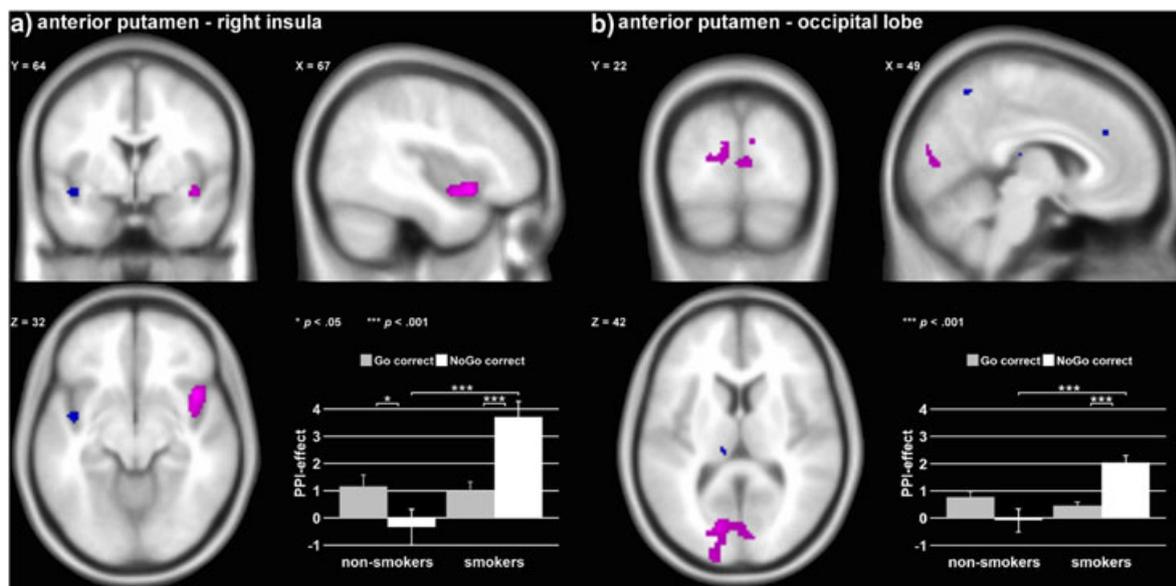
Figure 1 a) Group difference in right insula cluster. b) Group difference in occipital lobe. In pink, results are shown at a cluster-level $p \leq .05$, FWE corrected for multiple comparisons across the whole brain, combined with a voxel-level threshold of uncorrected $p < .001$. In blue, results are shown at a voxel-level threshold of uncorrected $p < .001$, without the cluster correction. Results are overlaid on the MNI 152 T1 template. The bar plots represent the PPI-effects for smokers compared to non-smokers. Group means with their standard errors are displayed for each condition (Go correct and NoGo correct). The values on the y-axis represent PPI-effects of the respective condition relative to baseline. The comparison non-smokers > smokers yielded no significant results at the threshold with FWE correction.

$t(36.71) = 4.28$, $p < .001$). We also contrasted the conditions in smokers and non-smokers separately. For smokers, the connectivity between the anterior putamen and the right insula and occipital lobe was stronger during NoGo correct trials compared to Go correct trials (right insula: $t(24) = 5.36$, $p < .001$; occipital lobe: $t(24) = 5.45$, $p < .001$), whereas for non-smokers there was a significant difference between conditions for the right insula only (right insula: $t(22) = 2.11$, $p = .046$, occipital lobe: $t(22) = 1.92$, $p = .068$). For the posterior putamen, no significant group differences were found. In Table S2, results are described at the more liberal threshold of voxel-level uncorrected $p < .001$. Here post hoc t-tests were not performed. An additional analysis described in the supplement confirmed that session order did not significantly influence our results.

Correlations with behaviour

To explore whether group differences were explained by individual differences in behaviour, we examined Pearson correlations of the extracted PPI-effects with the behavioural variables. Because the group differences in PPI-effects were driven by the NoGo correct trials, we only computed correlations with the connectivity during NoGo correct trials. No significant relationships emerged between connectivity of the occipital cluster and Go RT ($r = .16$, $p = .266$), NoGo accuracy ($r = .09$, $p = .538$) or BIS-11 total score ($r = .17$, $p = .244$). The right insula cluster had no associations with Go RT ($r = .23$, $p = .111$) or NoGo accuracy ($r = .00$, $p = .981$), but did show a relationship with BIS-11 total score ($r = .33$, $p = .024$). Participants with a higher total score on the BIS-11, reflecting higher trait impulsivity, showed higher connectivity between the anterior putamen and the right insula during NoGo correct trials (see Figure 2). However, this result did not survive correction for multiple comparisons using a corrected α of .013 (.05 divided by 3.9, the 'effective number', M(eff), of independent tests). Furthermore, for smokers ($n = 25$) there were no significant associations between connectivity during NoGo correct trials and FTND nicotine dependence scores (occipital: $r = -.05$, $p = .796$; right insula: $r = -.16$, $p = .433$) or QSU scores for smoking urges (occipital: $r = -.19$, $p = .367$; right insula: $r = -.19$, $p = .363$). Table 3 displays descriptive statistics of the above variables for smokers and non-smokers separately, along with the corresponding tests for differences in means. As seen in Table 3, smokers did not differ on NoGo accuracy, but had longer Go RTs and higher BIS-11 total scores for trait impulsivity. Performance was not significantly affected by session order (see supplement).
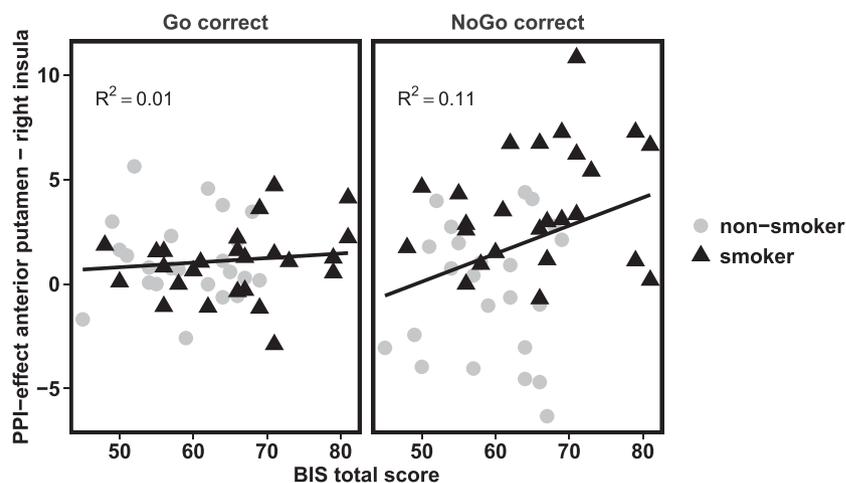
Figure 2 Correlation between BIS-11 total score (trait impulsivity) and PPI-effects of the anterior putamen with the right insula. Separate plots are displayed for the PPI-effects during Go correct trials and during NoGo correct trials.

Table 3 Descriptive statistics of behavioural measures.

	Smokers	Non-smokers	Difference smokers versus non-smokers[a]
NoGo accuracy M(SD)	60.69 (14.23)	61.74 (15.06)	$t(46) = 1.05$, $p = .805$
Go reaction time M(SD)	371.04 (51.49)	340.47 (46.42)	$t(46) = 2.15$, $p = .037$
BIS-11 total scores[b] M(SD)	65.52 (9.28)	59.04 (6.87)	$t(46) = 2.73$, $p = .009$
QSU scores[c] M(SD)	39.71 (11.48)	n/a	n/a

[a]To test for significant differences, independent samples t-tests were used. [b]BIS-11 total scores can range from 30 to 120. [c]QSU-scores can range from 10 to 50. Note: these data overlap with those reported in a previous study of this sample (Luijten *et al.* 2013).

DISCUSSION

The first aim of the present study was to investigate functional networks of the anterior and posterior putamen in a Go–NoGo paradigm. During inhibition compared to repetitive responding, we observed the hypothesized stronger connectivity between the anterior putamen and a large cluster in the frontal lobe, including the ACC and medial frontal regions. Additionally, a cluster was revealed in the precuneus, an area that has been increasingly acknowledged as an important hub for high-order cognitive functions requiring sensorimotor integration and voluntary shifts of attention (Cavanna & Trimble 2006). The ACC and precuneus have been commonly found to be activated during inhibition in Go–NoGo tasks (Garavan *et al.* 2006; Swick, Ashley & Turken 2011), and both regions have been associated with performance-monitoring during these tasks (Menon *et al.* 2001). Our results are in line with previous studies demonstrating a distinct pattern of activation of the anterior putamen and concurrent activation of frontal regions during the early stages of motor learning, when demands on response-monitoring are higher (Jueptner *et al.* 1997; Lehéricy *et al.* 2005). Furthermore, similar activation patterns have been observed in relation to goal-directed responding during instrumental learning (Sjoerds *et al.* 2013; Tricomi, Balleine & O'Doherty 2009). Although structural and resting state studies have also confirmed connectivity between the anterior putamen and ACC (Di Martino *et al.* 2008; Draganski *et al.* 2008; Haber 2003; Lehéricy *et al.* 2004), we believe to be the first to isolate connectivity of this network in a response inhibition paradigm. This finding adds to the response inhibition literature by highlighting the important role of the anterior putamen network during inhibition. Together, the current results and the findings reviewed above indicate that the anterior putamen is involved in a frontal network that is more strongly recruited during a range of conditions requiring response-monitoring or goal-directed control as opposed to conditions that are more automatic or habitual.

Also in keeping with this specialization of the anterior putamen, the posterior putamen displayed no connectivity with these frontal regions during inhibition. Instead, clusters emerged in the parietal and occipital lobes and on the border of the pre- and postcentral gyri. This pattern confirms the view of the posterior putamen as a 'sensorimotor' region (de Wit *et al.* 2012; Gillan *et al.* 2016). However, there were no sensorimotor clusters that showed heightened connectivity with the posterior putamen during repetitive responding, which contrasts with our expectation based on literature demonstrating that the posterior putamen is involved in habits and over-learned actions. Studies on motor and instrumental learning have consistently observed greater activation of the posterior putamen and stronger connectivity with sensorimotor regions in relation to stronger learned motor responses (Jueptner *et al.* 1997; Lehéricy *et al.* 2005; Wu, Chan & Hallett 2008) or stimulus–response associations (Horga *et al.* 2015; Sjoerds *et al.* 2013; Tricomi, Balleine & O'Doherty 2009). This indicates that the posterior putamen is engaged in establishing stimulus–response relationships, and that the strength and influence of these relationships increase with additional learning. Knowledge of posterior putamen network connectivity in other experimental contexts, such as the Go–NoGo task, is currently lacking. Our results suggest that it remains challenging to isolate habit-related processes, and that automatic responding seen during often time-consuming motor and instrumental learning paradigms cannot simply be extrapolated to repetitive Go-responding. We hypothesize that different dynamics play a role in the Go–NoGo task, which consists of explicit stimulus–response relationships that are assumed to be equally well-learned. Following from the results, it seems that the infrequent switches of stimulus–response pattern in NoGo trials recruit connectivity of both the goal-directed and the habitual/sensorimotor putamen networks to a greater extent than the frequent Go trials. However, there could still be differences in the relative contribution of these networks over time or over sub-groups of individuals.

Indeed, our next aim was to compare smokers to non-smokers on the connectivity within anterior and posterior putamen networks during inhibition. We expected that smokers would exhibit lower functional connectivity between the anterior putamen and frontal areas such as the ACC, reflecting a relatively weak goal-directed control network. Disturbed response-monitoring in the ACC during inhibitory control has been suggested to constitute one of the core deficits of addiction (Luijten *et al.* 2014), and evidence for hypoactivity of the ACC has been found in the current sample of smokers (Luijten *et al.* 2013). However, even though substantial inhibition-related connectivity was observed between the anterior putamen and ACC across all participants, there was no difference in this connectivity between smokers and non-smokers. This finding diverges from the study by Hong *et al.* (2009), where weaker connectivity between striatum and ACC during resting-state was related to higher nicotine dependence scores. Also, weaker connectivity between putamen and ACC during inhibition was seen in alcohol dependent individuals (Courtney, Ghahremani & Ray 2012). Because to our knowledge, this is the first study to examine putamen connectivity in smokers within an inhibitory control paradigm, further research is required to clarify these contrasting findings.

An unexpected significant group difference emerged for the inhibition-related connectivity, where smokers

displayed higher connectivity than non-smokers between the anterior putamen and clusters in the right insula and occipital lobe. The insula has been consistently linked to performance on inhibitory control tasks (Cai *et al.* 2014), nicotine dependence, craving (Naqvi *et al.* 2014) and trait impulsivity (Churchwell & Yurgelun-Todd 2013; Moreno-López *et al.* 2012). Interestingly, lesions of both putamen and insula (separately or together) have been found to cause spontaneous smoking cessation (Gaznick *et al.* 2014). The fact that smokers had unimpaired accuracy rates, but longer reaction times, could imply that alternative strategies were used or that networks were recruited less efficiently. However, we did not find an association between reaction times and connectivity measures. Instead, a tentative correlation was observed between anterior putamen – right insula connectivity and trait impulsivity scores across smokers and non-smokers. Although this result warrants replication, we are inclined to attribute the obtained difference between smokers and non-smokers in insula connectivity to individual differences in trait impulsivity. High trait impulsivity may lead to an increased probability of smoking initiation (O'Loughlin *et al.* 2009) and heightened susceptibility to proceed to compulsive behaviour (Belin *et al.* 2016). Notably, previous studies have also shown disturbances in connectivity of the insula with the ACC in smokers (Janes *et al.* 2015; Zanchi *et al.* 2015), and these regions are both part of the salience network (Uddin 2015). In sum, evidence for salience network (insula, ACC) and putamen dysfunction in addiction is accumulating (Everitt & Robbins 2016), although the direction of effects is not always consistent and may depend on the type of addiction, demands of the task, and the outcome measures under study (e.g. activity or connectivity). Further studies could explore whether differences in functional connectivity are codetermined by differences in white matter connectivity.

Concerning the posterior putamen network, the hypothesis of a relatively strong influence or interference of this network during inhibition in smokers could not be confirmed. As discussed above, it seems that both groups recruited the posterior putamen sensorimotor network to a greater extent during inhibition compared to repetitive responding. Perhaps group differences only become visible when smokers are confronted with drug-related cues. Indeed, in some studies smokers displayed higher motor and dorsal striatal reactivity to smoking cues than non-smokers (Jasinska *et al.* 2014), although an overreliance on the habit system has been demonstrated in alcohol dependent individuals using neutral cues (Sjoerds *et al.* 2013). Alternatively, our moderate sample size of 25 versus 23 may have resulted in insufficient power to detect small differences between the groups. So far, studies directly investigating habit

formation and expression in human participants with addiction are scarce and no golden standard exist (Sjoerds *et al.* 2014). This calls for more research devoted to this topic.

To summarize, the present findings support the hypothesis of enhanced anterior putamen – frontal (ACC) synchronization during inhibition. The posterior putamen showed stronger connectivity with sensorimotor regions, in line with literature referring to this region as the sensorimotor putamen. The expected heightened connectivity of this network during repetitive responding was not observed, presumably because of different network dynamics in Go–NoGo tasks compared to learning tasks. The results extend on previous findings by confirming for the first time in a response inhibition paradigm, the involvement of anterior putamen – frontal connectivity in contexts requiring response-monitoring or goal-directed responding. Furthermore, it underscores the importance of considering functional subdivisions of the putamen when performing connectivity analyses. In contrast to the hypothesized weaker anterior putamen – ACC connectivity during inhibition, our study revealed a disturbed anterior putamen – insula connection in smokers, and a tentative relationship of the synchronized activity of these regions with trait impulsivity. This finding highlights the role of the insula in nicotine addiction and in impulsive–compulsive behaviour. Moreover, it indicates that it would be worthwhile for future studies to examine interactions between insula and anterior putamen in the context of inhibitory control and addiction.

Acknowledgements

Authors Contribution

SEAA, ML, IHAF and JKB were responsible for the study concept and design. ML acquired the fMRI data and

performed the standard fMRI analyses. SEAA performed the functional connectivity analyses. ML and DvR assisted with data analysis and interpretation of findings. SEAA drafted the manuscript. ML, DvR, IHAF and JKB provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved the final version for publication.

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