Right Prefrontal and Ventral Striatum Interactions Underlying Impulsive Choice and Impulsive Responding

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Abstract: Although a multifaceted concept, many forms of impulsivity may originate from interactions between prefrontally-mediated cognitive control mechanisms and limbic, reward or incentive salience approach processes. We describe a novel task that combines reward and control processes to probe this putative interaction. The task involves elements of the monetary incentive delay task (Knutson et al., [2000]: *Neuroimage* 12:20–27) and the Go/No-Go task (Garavan et al., [1999]: *Neuroimage* 17:1820–1829) and requires human subjects to make fast responses to targets for financial reward but to occasionally inhibit responding when a NoGo signal rather than a target is presented. In elucidating the dynamic between reward anticipation and control we observed that successful inhibitions on monetary trials, relative to unsuccessful inhibitions, were associated, during the anticipation phase, with increased activation in the right inferior frontal gyrus (rIFG), decreased activity in the ventral striatum (VS), and altered functional connectivity between the two. Notably, this rIFG area had a small overlap but was largely distinct from an adjacent rIFG region that was active for the subsequent motor response inhibitions. Combined, the results suggest a role for adjacent regions of the rIFG in impulsive choice and in impulsive responding and identify a functional coupling between the rIFG and the VS. *Hum Brain Mapp* 36:187–198, 2015. © 2014 Wiley Periodicals, Inc.

Key words: impulsivity; response inhibition; reward; right inferior frontal gyrus; ventral striatum; functional connectivity

INTRODUCTION

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Although impulsivity is a multifaceted trait, characterizations often include actions that are poorly conceived, made without forethought of their appropriateness and lack a full consideration of their consequences [Evenden, 1999]. Laboratory-based methods attempting to measure impulsivity range from self-report measures [e.g., Barratt Impulsivity Scale, (BIS); Patton et al., 1995], to tasks that assess motor response countermanding [Logan et al., 1997], information selection prior to a decision [Kagan, 1966], and delaying gratification measured using the delay discounting paradigm [Kirby and Maraković, 1996]. With the multiplicity of measures available and the observation

that several of these correlate poorly with each other [Dalley et al., 2011], it is quite plausible that there may exist numerous brain systems subserving different aspects of behavior. Many of the essential aspects of impulsivity may reflect an antagonistic dual system wherein impulsive behavior is guided by the interactions between an impulsive system and a reflective system [Hofmann et al., 2009]. Here, the latter is proposed to serve a regulatory role, while the former is thought responsible for motivating an approach behavior that may need to be regulated.

A prime candidate for playing a major role in a reflective, cognitive control system is the prefrontal cortex [PFC; Miller and Cohen, 2001]. Tasks that measure the ability of a person to inhibit a prepotent motor response (e.g., STOP-Signal and Go/No-Go tasks) can be used to assay this control and reliably activate the PFC [Chikazoe, 2010; Whelan et al., 2012]. Conversely, the striatum, particularly the ventral portion, may play an important role in the theorized impulsive system. The striatum is a subcortical structure that tends to be divided into two segments: a ventral component comprising the olfactory tubercle, nucleus accumbens (NAcc), and ventromedial portions of the caudate and putamen, and a dorsal component encompassing the remainder of the caudate and putamen [Delgado, 2007]. The ventral striatum (VS) has been linked to the drive for immediate reward gratification [McClure et al., 2004] and impulsive responding [Dalley et al., 2007] and this region has been shown to be activated during the anticipation of a financial reward in a monetary incentive delay (MID) task [Knutson et al., 2000]. In addition, striatal activation tends to accompany response inhibition [Aron and Poldrack, 2006; Zandbelt and Vink, 2010] which has been suggested is indicative of its role in an “indirect” pathway connecting frontal cortical activation to motor output [Nambu et al., 2002], although such activation tends to be associated more with dorsal portions of the striatum such as the putamen and posterior caudate.

Relatively few studies have examined connections between the impulsive and regulatory systems. Diekhof and Gruber [2010] reported an increased negative correlation between the PFC and VS when participants selected in favor of a long-term goal over a more immediate reward. The magnitude of the negative correlation was itself correlated with the aforementioned BIS and the novelty-seeking scale of the Temperament and Character Inventory [Cloninger et al., 1993]. Similarly, an emotion regulation (ER) study demonstrated decreased VS activation and increased left frontal activation during a cue period prior to a potential monetary reward in which participants were instructed to regulate their expectation of reward [Delgado et al., 2008]. Unfortunately, no attempts to functionally connect the two areas were reported. Conversely, Staudinger et al. [2011] did perform such a connectivity analyses with a similar paradigm in which participants used cognitive ER prior to monetary gain and showed dorsolateral PFC activity correlating more positively with putamen activity prior to a small monetary

gain compared to a large monetary gain. A more recent study has also highlighted similar frontostriatal interactions with striatal dopamine D2-type receptor availability negatively correlating with activation levels in dorsolateral prefrontal regions during a risk-taking scenario [Kohn et al., *in press*].

We postulate that impulsive actions are dictated by an interplay between a PFC regulatory system involved in top-down cognitive control and a VS-based impulsive system concerned with reinforcement. We attempt to assay this interaction with a novel task that combines aspects of well-established tasks that are known to activate these regions of interest. The task couples reward anticipation, as assayed by the MID task [Knutson et al., 2000] with response inhibition processes, as assayed by the Go/NoGo paradigm [Garavan et al., 1999]. In addition to providing separate activation measures for both processes, it also combines the two such that participants are required to regulate their reward anticipation which we predict will be reflected in a prefrontal modulation of striatal activation levels. Unlike previous studies, the task also enables us to determine if the same prefrontal regions that underlie response inhibition also regulate reward anticipation. There is evidence that the right PFC’s role in inhibitory control may extend beyond motor response inhibition processes to include the suppression of memories and drug cravings [Depue et al., 2007; Tabibnia et al., 2011; Volkow et al., 2010]. Although this structure’s role in cognitive control may extend beyond inhibition [Hampshire et al., 2010] it is of theoretical importance to determine if it is a common node in the two main domains of impulsive choice and impulsive responding, with the former typically representing reward-related choices characterized by the desire for immediate rewards and the latter representing control over motor responses.

METHODS

Participants

Twenty right-handed participants (11 female, mean age: 23.05, range 18–35) took part in the experiment. Participants were screened for no history of neurological/psychiatric illness or any past loss of consciousness which required hospitalization. All participants were right-handed. All participants gave informed consent and the study was approved by the School of Psychology in Trinity College Dublin. Participants were financially compensated for their time.

Stimuli and Behavioral Protocol

Monetary incentive delay-Go/NoGoTask

In the MID-Go/NoGo task (Fig. 1), a cue in the form of either a square or circle was presented on screen for between 2 and 8 s, with color coding for the possibility of

Figure 1.

The MID-Go/NoGo Task. A cue in the form of either a square or circle was presented on screen for between 2 and 8 s, with color coding for the possibility of obtaining a monetary reward (green) or not (blue). Targets (a star within a circle) appeared after all square cue periods and half the time after circle cues. Participants were required to respond on presentation of the target. Following 50% of the circle cues, a NoGo signal was presented instead of a target and participants were required to inhibit their response. Trials on which a target always followed the cue (i.e., squares) were termed MID trials. Trials on which a response withhold was required (i.e., NoGo signals presented after circles) were termed MID-NoGo trials with the remaining trial types (targets presented after circles) classified as MID-Go trials. A response to a target during its presentation was considered a HIT and yielded a financial reward (green trials; 20 cent), whereas a lack of response was considered a MISS and no financial reward was obtained. There were no financial consequences

for HITS and MISSES on neutral trials (blue trials). Targets were initially presented for 400 ms with an adaptive algorithm reducing the target duration by 50 ms following a HIT, and increasing it by 50 ms following a MISS. For reward MID-NoGo trials, a response was considered a MID-NoGo_{Error} and incurred a financial loss (40 cent), whereas successful inhibitions were classified as a MID-NoGo_{Success} and yielded a financial reward (20 cent). There were no financial consequences on neutral MID-NoGo trials. The response duration for MID-NoGo trials was set at 600 ms for all trials. For trials containing targets, feedback was displayed for a period dictated by the adaptive algorithm (2000 ms minus the RT window of the target). Feedback was displayed for 1400 ms for trials containing NoGo signals. A fixation cross was presented for between 2–8 s before the next trial commenced. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

obtaining a monetary reward (green) or not (blue). Targets (a star within a circle) appeared after the presentation of all square cue periods and half the time after the presentation of circle cue periods. Participants were required to respond on presentation of the target. The other 50% of the time after circle cues, a NoGo signal was presented instead of a target and participants were required to inhibit their response. Trials on which a target was always bound to follow the cue (i.e., squares) are hereafter termed MID trials. Trials on which a response withhold is required (i.e., NoGo signals presented after circles) are, hereafter, termed MID-NoGo trials with the remaining trial types (targets presented after circles) being classified as MID-Go trials. There were 25 trials of each type (25 reward MID, 25 neutral MID, 25 reward MID-Go, 25 neu-

tral MID-Go, and 25 reward MID-NoGo, 25 neutral MID-NoGo).

A response to a target during its presentation was considered a HIT and yielded a financial reward (green trials; 20 cent), whereas a lack of response was considered a MISS and no financial reward was obtained. There were no financial consequences for HITS and MISSES on neutral trials (blue trials). Targets were initially presented for 400 ms with an adaptive algorithm reducing the target duration by 50 ms following a HIT, and increasing it by 50 ms following a MISS. For reward MID-NoGo trials, a response was considered a MID-NoGo_{Error} and incurred a financial loss (40 cent), whereas successful inhibitions were classified as a MID-NoGo_{Success} and yielded a financial reward (20 cent). These values were chosen so as to ensure that

the failure to inhibit a response was financially costly; this, we hypothesized, would encourage participants to modulate the reward anticipation processes during the cue period. This reward asymmetry also ensured that subjects prioritized successful inhibitions and would therefore reveal the hypothesized top-down regulation of reward/reinforcement systems. There were no financial consequences on neutral MID-NoGo trials. The response duration for MID-NoGo trials was set at 600 ms. For trials containing targets, feedback was displayed for a period dictated by the adaptive algorithm (2000 ms minus the response time (RT) window of the target). Feedback was displayed for 1400 ms for MID-NoGo trials. A fixation cross was presented for between 2–8 s before the next trial commenced. The mean jitter for cue periods was 4 s, and the mean jitter for the interstimulus interval was 5.2 s.

Participants were informed that their performance on the task would determine their level of winnings. Prior to scanning, the task was demonstrated to all participants and participants also practiced the task themselves. There was a total of 30 trials in each run (five of each type of cue period) presented in random order. There were five runs of the task in total, with each run lasting 352 s. Response times and percentage accuracy were recorded for each trial. The experiment was programmed and run using Presentation software® (Version 14.1, www.neurobs.com).

Imaging Parameters

Scanning was conducted on a Philips Intera Achieva 3.0 T MR system (Best, The Netherlands). A coil-mounted mirror reflected a 800×600 pixel display that was projected onto a panel behind the participant's head outside the magnet.

An initial reference scan allowed for the resolution of sensitivity variations. All imaging utilized a parallel sensitivity encoding approach with a reduction factor of 2 [Pruessmann et al., 1999].

180 high-resolution T1-weighted anatomic MPRAGE transverse images (field-of-view (FOV) 230 mm, thickness 0.9 mm, voxel size $0.9 \times 0.9 \times 0.9$) were then acquired (total duration 343 s) to allow subsequent activation localization and spatial normalization.

39 noncontiguous (0.35 mm gap) 3.5 mm transverse slices covering the entire brain were acquired using a T2* weighted echo-planar imaging sequence (TR = 2000 ms, TE = 30 ms, FOV 224 mm, 64×64 matrix size in Fourier space). Functional scans had a total duration of 358 s per run.

Time-Series Analysis

Functional magnetic resonance imaging (fMRI) data analyses were conducted using AFNI software [Cox, 1996; <http://afni.nimh.nih.gov/afni>]. Data were corrected for slice time acquisition and motion-corrected using three-

dimensional volume registration (least-squares alignment of three translational and three rotational parameters). All five runs of the task were concatenated and subsequent edge detection algorithms were used to remove activation outside of the brain.

General linear modeling analysis involved estimating activation measures for eight cue period types: reward and neutral square cue periods (MID trials), reward and neutral circle cue periods that were followed by targets (MID-Go trials) and reward and neutral circle cue periods that were followed by NoGo signals (MID-NoGo trials). Reward and neutral MID-NoGo cue periods were split into two types depending on whether participants subsequently successfully inhibited (MID-NoGo_{Success} cue period) or not (MID-NoGo_{Error} cue period). Activations for twelve outcome periods (comprising both the target/STOP and associated feedback) were also estimated: HITS and MISSES for reward and neutral cue periods which were followed by targets (i.e., MID and MID-Go trials), and MID-NoGo_{Success} and MID-NoGo_{Error} for reward and neutral cue periods which were followed by NoGo signals (i.e., MID-NoGo trials). Six motion regressors, comprising three axes of rotation and three directions of translation, were also included as nuisance covariates.

Regression analyses calculated activation for cue periods as a percentage change relative to the baseline (the fixation periods between trials). These activation maps were warped into standard Talairach space [Talairach and Tournoux, 1988] and spatially smoothed with a 4.2 mm full-width at half-maximum isotropic Gaussian kernel. Group activation maps for each cue period were calculated with one-sample *t*-tests against the null hypothesis of zero activation change. To identify the regions associated with reward anticipation, a voxelwise paired *t*-test compared reward and neutral MID trial cue periods. Further to this, to verify that reinforcement-associated regions of the VS were activated during the anticipation of a reward [Knutson et al., 2001], mean activation values for reward and neutral MID trial cue periods were extracted from 2 mm radius spheres constructed around the central coordinates of bilateral NAcc regions (right NAcc: 11,11,0; left NAcc: -8, 12, 0), and compared with paired *t*-tests. To identify cue period predictors of successful inhibition, a voxelwise paired *t*-test compared reward MID-NoGo_{Success} and MID-NoGo_{Error} cue periods. For all analyses, significant voxels passed a voxelwise statistical threshold ($t = 3.17$, $P \leq 0.005$) and were required to be part of a larger 281 μ l cluster of contiguous voxels to arrive at a cluster-level threshold of $P \leq 0.05$, corrected. A series of Monte Carlo simulations (1,000 iterations) were performed to determine cluster sizes.

To assess outcome-related activations, distinct event-related haemodynamic response functions at 2 s temporal resolution were calculated using deconvolution techniques. The haemodynamic response functions were then modeled voxelwise with a gamma-variate function using nonlinear regression [Murphy and Garavan, 2005]. An area-under-

the-curve measure of the gamma-variate model was expressed as a percentage of the tonic baseline activity (an implicit baseline that reflects ongoing task-related processes not explicitly coded by one of the regressors) and served as the activation measure for these event-related responses. Activation maps were warped and spatially blurred, as above. Group activation maps for each outcome were created with one-sample *t*-tests.

Psychophysiological Interaction Analysis

Psychophysiological interaction (PPI) analysis [Friston et al., 1997] was used to investigate whether functional connections between frontal and striatal regions differed prior to a MID-NoGo_{Success} and a MID-NoGo_{Error} on reward-related trials and to also identify whole-brain functional connections between a response inhibition-related right inferior frontal gyrus (rIFG) region during successful inhibitions on these trials. In the first instance, a rIFG region, identified from the voxelwise reward MID-NoGo_{Success} versus reward MID-NoGo_{Error} cue period *t*-test, was chosen as the seed region and its time series served as the physiological regressor. Psychological regressors coded for the time periods of interest (namely, reward MID-NoGo_{Success} and reward MID-NoGo_{Error} cue periods). To create the PPI term, the physiological regressor was first deconvolved (the rationale for the deconvolution step is that the PPI occurs at the neuronal and not the haemodynamic BOLD level), the interaction with the psychological regressor was calculated, this was then convolved with a standard haemodynamic response to create the PPI term which, finally, was mean-corrected. The physiological regressor, PPI term and psychological regressor were entered into a regression analysis along with all the other cue periods and outcomes in the task and *z*-scores for the PPI term were obtained. These *z*-scores were normalized and spatially smoothed, as described above. Whole-brain, one-sample voxelwise *t*-tests were run on these *z*-scores and corrections for multiple comparisons were the same as above. In the second instance, a rIFG region, identified from a voxelwise one-sample *t*-test of reward MID-NoGo_{Success} outcomes against the null hypothesis of zero activation change, was chosen as a seed region. The psychological regressor coded for when participants successfully inhibited on reward MID-NoGo trials (i.e., MID-NoGo_{Success} outcome periods). The remainder of the PPI analysis was as above.

Statistical Analysis

Behavioral data were analyzed with the statistical package SPSS (version 16). Two-factor (cue condition $\times$ reward/neutral) repeated measures analysis of variance (ANOVA) were used to compare accuracy and RT differences on targets (i.e., MID and MID-Go trials). Paired *t*-tests compared % successful inhibition and commission

Figure 2.

Average % accuracy (%HITs) and reaction times (RTs) for targets on MID and MID-Go trials.

error reaction time differences between reward and neutral cue periods that were followed by NoGo signals (i.e., MID-NoGo trials).

RESULTS

Behavioral Results

The potential presence of a NoGo signal affects both % accuracy and response time

Figure 2 displays accuracy (% HITS) and mean RTs for the reward and neutral MID trials and MID-Go trials. Behavioral accuracy was not close to 100% in reward MID trials due to the tracking adaptive algorithm in place. A 2 (cue condition) $\times$ 2 (reward/neutral) repeated measures ANOVA for accuracy found a significant effect for cue condition (MID cue > MID-Go cue; $F_{1,19} = 20.61$, $P < 0.001$), a significant effect of reward (Reward > Neutral; $F_{1,19} = 44.383$, $P < 0.001$), but no interaction ($F_{1,19} = 1.01$, $P = 0.73$). There was no difference in % successful inhibitions between the reward and neutral MID-NoGo trials ($t(19) = 1.21$, $P = 0.24$). Participants successfully inhibited $73 \pm 3.59\%$ of the time on reward MID-NoGo trials and $76 \pm 3.01\%$ on neutral MID-NoGo trials.

A 2 (cue condition) $\times$ 2 (reward/neutral) repeated measures ANOVA on RTs found a significant effect for cue condition (MID cue faster than MID-Go cue; $F_{1,19} = 27.75$, $P < 0.001$), a significant effect of reward (Reward faster than Neutral; $F_{1,19} = 59.231$, $P < 0.000001$),

TABLE I. Regions of activation from a voxelwise *t*-test between reward and neutral MID cue periods

Structure	Hemisphere	Volume (μ l)	Brodmann area	x	y	z
Frontal						
Medial frontal gyrus	Right	5999	6	1	-3	56
Orbitofrontal cortex (right medial frontal gyrus)	Right	1075	10/32	15	39	-8
Middle frontal gyrus	Right	393	9	31	36	35
Middle frontal gyrus	Left	469	9	-30	32	37
Postcentral gyrus	Left	6748	4	-39	-20	54
Limbic						
Parahippocampal gyrus/amygdala	Left	340	34	-20	-6	-13
Striatum						
Caudate (ventral striatum)	Right	2878		12	11	6
Caudate (ventral striatum)	Left	2568		-14	7	10
Lentiform nucleus and putamen	Left	314		-23	-4	2
Parietal						
Precuneus	Left	807	7	-11	-72	43
Paracentral lobule	Left	769	4	-8	-37	59
Occipital						
Lingual Gyrus	Right	6613	18	23	-91	-5
Lingual Gyrus	Left	3490	18	-24	-91	-6
Cerebellum						
Culmen	Right	3075		23	-51	-21
Cerebellar tonsil	Right	1239		39	-47	-31

Positive values for *x*, *y*, and *z* Talairach coordinates identify the centre of mass of each cluster and denote, respectively, locations that are right, anterior and superior relative to the anterior commissure. All areas exhibited more activation during reward MID cue periods, except for the left parahippocampal gyrus/amygdala which was more active during neutral MID cue periods.

but no interaction ($F_{1,19} = 0.09$, $P = 0.76$). There was no difference in commission error RTs between the reward (293.4 ± 8.23) and neutral (314.24 ± 10.63) MID-NoGo trials ($t(19) = 1.67$, $P = 0.11$).

Combined, these results demonstrate that the presence of reward improved performance while the possibility of a response inhibition led to slower responses.

Functional Magnetic Resonance Imaging Results

The MID-Go/NoGo task reliably activates the ventral striatum

To demonstrate that the prospect of a financial reward activated reward/reinforcement circuitry, as evidenced in other studies utilizing the MID task [Knutson et al., 2000], a voxelwise *t*-test compared reward and neutral MID cue periods (i.e., the anticipation periods that were never potentially followed by a NoGo signal). Greater cue period activation was observed for the reward trials, particularly in bilateral medial VS areas and in the left putamen [Table I and Fig. 3a] and also in motor and visual areas. Follow-up region-of-interest analysis aimed to determine whether the NAcc, an area considered to be the portion of the striatum most related to reinforcement-seeking behavior [Delgado, 2007; Haber and Knutson, 2010], was activated during the prospect of a reward. Bilateral NAcc regions, previously demonstrated to become activated during the anticipation of a reward [Knutson et al., 2001], were significantly more active during a reward MID cue

period compared to a neutral MID cue period (right NAcc: $t(19) = 4.645$, $P \leq 0.0005$, left NAcc: $t(19) = 2.708$, $P \leq 0.01$). This was in line with previous studies reporting elevated NAcc activation patterns during the reward anticipation cue period of the MID paradigm [Knutson et al., 2000, 2001].

Predictors of successful response inhibition

Next, we investigated the cue period activity that preceded successful and unsuccessful response inhibitions in reward-related MID-NoGo trials. This contrast was chosen to identify regions specifically linked to the putative regulatory system—we reasoned that this regulation would be greater prior to a successful inhibition relative to a subsequent failure to inhibit. A voxelwise *t*-test compared reward MID-NoGo cue periods that were split according to subsequent behavior (i.e., MID-NoGo_{Success} cue periods and MID-NoGo_{Error} cue periods). As reported in Table II and shown in Figure 3b, the left inferior parietal lobule and a rIFG region that extends into the anterior insula and encompasses some surrounding white matter—BA 44—both demonstrated increased activation during the reward MID-NoGo_{Success} cue period while, conversely, the left caudate (VS) exhibited more activation during the reward MID-NoGo_{Error} cue period. Given a priori interest in rIFG as a critical node for inhibitory control, we aimed to determine whether this rIFG activity was unique to reward MID-NoGo cue periods or whether it was also engaged during neutral MID-NoGo cue period (i.e., was it activated

Figure 3.

(a) Bilateral ventral striatal regions showing more activation preceding a reward target compared to a neutral target during MID trials. (b) The right IFG showed significantly more activation during a reward MID-NoGo_{Success} cue period compared to a reward MID-NoGo_{Error} cue period while the left caudate (VS) showed the opposite. (c) Left ventral striatal regions which displayed significant differences in functional connectivity with the rIFG during reward MID-NoGo_{Success} and reward MID-NoGo_{Error} cue periods. Mean activation patterns from each region during these cue periods are plotted. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

played significant differences in functional connectivity with the rIFG during reward MID-NoGo_{Success} and reward MID-NoGo_{Error} cue periods. Mean activation patterns from each region during these cue periods are plotted. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

prior to any successful inhibition or was it specifically engaged prior to a successful inhibition on those trials in which there was the prospect of a reward). A 2 (reward/neutral) $\pm$ 2 (MID-NoGo_{Success}/MID-NoGo_{Error}) repeated measures ANOVA determined that there was a significant interaction effect $F_{1,19} = 10.883$, $P < 0.004$ with rIFG activity changing as a function of subsequent behavior (successful

inhibition/error) during reward MID-NoGo cue periods but not during neutral MID-NoGo cue periods.

A PPI analysis was then conducted for this functionally-defined rIFG area with the reward MID-NoGo_{Success} and reward MID-NoGo_{Error} cue periods serving as the specific conditions of interest. With this contrast, we hoped to determine if the right prefrontal area, interpreted to

TABLE II. Regions of activation from a voxelwise t-test contrasting reward MID-NoGo cue periods prior to a successful inhibition (reward MID-NoGo_{Success} cue periods) against reward MID-NoGo cue periods prior to a commission error (reward MID-NoGo_{Error} cue periods)

Structure	Hemisphere	Volume (μ l)	Brodmann area	x	y	z
Inferior parietal lobule	Left	1503	19/39	-46	-61	37
Caudate (ventral striatum)	Left	877		-15	24	2
Inferior frontal gyrus	Right	285	44	39	14	17

Positive values for x , y , and z Talairach coordinates identify the centre of mass of each cluster and denote, respectively, locations that are right, anterior and superior relative to the anterior commissure. The left inferior parietal area and the right inferior frontal gyrus exhibited more activation during a reward MID-NoGo_{Success} cue period, while the caudate area demonstrated more activity during a reward MID-NoGo_{Error} cue period.

subserve a top-down regulatory process during reward MID-NoGo cue periods, would show correlated activity with brain regions, particularly VS, hypothesized to subserve the reward-related impulsivity. A whole-brain, voxelwise analysis revealed the rIFG to be significantly more negatively coupled with left ($-12, 21, 1$) and right VS ($12, 25, 8$) during a reward MID-NoGo_{Success} cue period compared to a reward MID-NoGo_{Error} cue period (see Fig. 3c). The right IFG was also more negatively coupled with regions in the cerebellum (inferior semi-lunar lobule), cuneus, lingual gyrus, and left inferior frontal gyrus during a reward MID-NoGo_{Success} cue period compared to a reward MID-NoGo_{Error} cue period. These VS areas overlapped with the left VS region shown above to be more active during the reward-related cue periods that preceded MID-NoGo_{Success} relative to MID-NoGo_{Error} (Fig. 3b) and also overlapped with the VS regions previously shown to be reward-related (Fig. 3a). We investigated whether the bilateral VS regions observed in the PPI analysis were reward-related by comparing activation patterns in these functionally-defined regions-of-interest during reward MID cue periods relative to neutral MID cue periods. The right VS demonstrated a significant difference ($t(19) = 2.928, P = 0.009$), while there was a similar trend for the left VS ($t(19) = 1.851, P = 0.08$).

Adjacent areas of the right inferior frontal cortex are active at the point of successful inhibition

Finally, as areas in the right inferior frontal cortex have previously been linked to response inhibition [Aron et al., 2003; Garavan et al., 1999], we investigated if the increased rIFG activation we had observed during the reward MID-NoGo_{Success} cue period was also active during motor inhibition. This contrast aimed to illustrate whether the activation during the cue period was linked more to impulsive choice rather than impulsive responding. A one-sample t -test of whole-brain event-related activation for successful inhibitions (i.e., reward MID-NoGo_{Success} outcomes) revealed activation in cingulate, parietal, cerebellar, and frontal regions including the rIFG. However, this lateral rIFG—BA 44 and 45—region was adjacent to the medial area whose activation was observed during the cue period (see Fig. 4) and, indeed, activity levels in this lateral functionally-defined region-of-interest did not differ between MID-NoGo_{Success} and MID-NoGo_{Error} cue periods ($t(19) = 1.51, P = 0.14$). Similarly, the rIFG region that did show cue-period activity was not significantly active at the time point of successful inhibition ($t(19) = 0.897, P = 0.38$). Finally, to identify whether this response inhibition-related right inferior frontal region exhibited functional connections with the VS during a successful inhibition on reward trials (i.e., a reward MID-NoGo_{Success} outcome), a PPI analysis was performed. Areas that were positively coupled with this region during a reward MID-NoGo_{Success} outcome included frontal, thalamic, parietal, and occipital cor-

Figure 4.

Adjacent but distinct regions of the rIFG were activated during response inhibition (green) and during reward MID-NoGo_{Success} cue periods (red). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

tex and are reported in Table III; there was no coupling with any VS regions.

DISCUSSION

Using a novel task, the current results reveal a functional coupling between right inferior frontal cortex and bilateral VS when an impulsive drive (the prospect of a monetary reward if one makes a sufficiently fast response) must be regulated to avoid a negative consequence (a financial loss if one executes the response when a response inhibition is required instead). At a behavioral level, the potential presence of a NoGo signal, and associated negative consequence, both slowed reaction times and reduced accuracy levels in certain trial types (MID-Go trials compared to MID trials) which indicates an element of proactive slowing so as to avoid the financial loss that accompanied responses on Stop trials. This proactive slowing is similar to other reports in which a precue informed participants that a STOP signal was highly likely to occur on the following trials [Hester et al., 2004; Fassbender et al., 2006; Jahfari et al., 2010; Vink et al., 2005; Verbruggen and Logan, 2009]. That a rIFG area was more active during a reward MID-NoGo_{Success} cue period, compared to a reward MID-NoGo_{Error} cue period, is in line with its supposed role in the neurobiology underlying proactive control. The rIFG has been linked to the development of such control with training on a stop-signal task being associated with increased engagement of this region during a cue period but decreased activation during the actual inhibition itself, when compared to activation patterns prior to

TABLE III. Regions that were (a) negatively coupled with the functionally-defined rIFG during a reward MID-NoGoSuccess cue period compared to a reward MID-NoGoError cue period, (b) positively coupled with a response inhibition-related lateral right inferior frontal gyrus region during a reward MID-NoGo_{Success} outcome

Structure	Hemisphere	Volume (μl)	Brodmann area	x	y	z
(a)						
Striatal						
Ventral striatum	Left	1892		-12	21	1
Ventral striatum	Right	593		12	25	8
Caudate tail	Left	375		-29	-40	11
Occipital						
Cuneus	Left	556		-13	-79	11
Cerebellar						
Uvula	Left	711		-14	-81	-34
(b)						
Frontal						
Middle frontal gyrus	Right	707	6	38	1	48
Superior frontal gyrus	Right	339	6	24	7	63
Thalamus						
Thalamus	Right	1023		4	-5	8
Parietal						
Inferior parietal lobule	Right	1981	40	41	-46	45
Superior parietal lobule	Right	322	7	29	-68	43
Occipital						
Fusiform gyrus	Left	2057	19	-31	-78	-14
Cuneus	Right	1029		24	-73	29
Middle occipital gyrus	Right	388	19	32	-79	9
Cerebellar						
Pyramis	Right	510		29	-83	-34

Positive values for x , y , and z Talairach co-ordinates identify the centre of mass of each cluster and denote, respectively, locations that are right, anterior, and superior relative to the anterior commissure.

the commencement of training [Berkman et al., 2014]. The area has also exhibited differential activation patterns between reactive and proactive control conditions during a working memory paradigm with embedded cues [Marlund and Persson, 2012] and also appears to display increased activation patterns associated with proactive control, but not reactive control, during brain development—from early adolescence to early adulthood [Vink et al., 2014]. Although the rIFG is frequently associated with proactive control, the VS, to our knowledge, does not tend to be engaged during this control. Thus, our MID-Go/NoGo task may be assaying proactive slowing with the additional dynamic of reward anticipation regulation. That the impulse control-related right prefrontal region was adjacent to, but largely anatomically separate from a right inferior frontal cortex activation that underlay motor response inhibition and which did not show any functional coupling with the VS further suggests that proactive control involving the potential suppression of a reward anticipation process may have been at play.

There are a number of lines of evidence pointing to roles for both the right PFC and the VS in impulsivity. Transcranial magnetic stimulation, lesion and neuroimaging studies link right PFC with successful response inhibition [Aron et al., 2003; Chambers et al., 2006; Garavan et al., 2002; Whelan et al., 2012]. Differences in the structural

integrity of the right ventromedial PFC have been shown to predict impulse control in a sample of male children [Boes et al., 2009] while impulse control deficits after frontal lobe injury are common [Bechara and Van der Linden, 2005]. Conversely, the VS is commonly associated with the representation of incentive or reward states [Knutson et al., 2000; Robinson and Berridge, 1993] whose aberrant functioning may lead to the occurrence of an impulsive drive. Studies, using animal models, have linked lesions of the VS to increased impulsive choice selection in a delayed reinforcement choice task in a rodent model [Cardinal et al., 2001], while an inverse relationship between dopamine D2/3 receptor availability in the VS and impulsivity (as characterized by premature responses on a five-choice serial reaction time task) has also been observed [Dalley et al., 2007]. Similarly, in humans, striatal dopaminergic availability has been linked to self-reported impulsiveness traits [Lee et al., 2009], as well as to the activity of response inhibition-related frontostriatal regions [Ghahremani et al., 2012]. However, lesions of the VS do not appear to affect stop-signal reaction times [Eagle and Robbins, 2003] indicating that discrete fronto-striatal circuits may be involved in different forms of impulsive behaviors. Pharmacological evidence also supports a dissociation of impulsive choice from impulsive responding—with noradrenergic transmission linked to the former and

serotonergic linked to the latter [Sun et al., 2012; Winstanley et al., 2004].

Evidence also points to interactions between the two areas to underlie impulsive choice selection. Individuals with a stronger preference for immediate over delayed rewards in an fMRI-based delay discounting paradigm demonstrated larger VS activations in response to monetary reward feedback [Hariri et al., 2006]. In the same study, PFC activations were also linked to regulating behavior on the task leading the authors to suggest that there may exist a “functional balance” between the two regions in relation to the selection of appropriate behavioral responses. In addition, there are known anatomical connections between prefrontal and ventral striatal regions [Leh et al., 2007], with prefrontal cortical thickness level shown to correlate with striatal dopamine release [Casey et al., 2013] and, complementing the present study’s functional connectivity findings, the strength of these anatomical connections predict better impulse control in a delay discounting paradigm [Peper et al., 2012].

Impulsivity is a multidimensional construct [Evenden, 1999] with impulsive choice selection often referring to a decision that is deficient in forethought of possible consequences, whereas impulsive response tends to refer to the execution of a response that is inappropriate [Basar et al., 2010]. As noted earlier, the right PFC is typically implicated in the countermanding of a prepotent motor response. However, its involvement in successful response inhibition has been linked to other functions including attentional monitoring and the detection and processing of salient cues [Chao et al., 2009; Dodds et al., 2011; Duann et al., 2009; Hampshire et al., 2010; Hester et al., 2004; Li et al., 2006; Sharp et al., 2010]. In line with our current results, the right PFC has also been linked to preparatory motor inhibition mechanisms [Hu and Li., 2012]. This involvement in motor inhibitory control may be just one example of a broader regulatory role that includes the modulation of subcortical functions [Munakata et al., 2011]. For example, successful suppression of drug cravings in cocaine-dependent individuals produced increased right inferior frontal gyral activation and decreased NAcc activity [Volkow et al., 2010]. Similarly, the ability to successfully suppress a memory linked the right inferior frontal cortex to interactions with subcortical structures, such as the thalamus and visual cortex [Depue et al., 2007]. Structurally, gray matter intensity in the pars opercularis portion of the rIFG was shown to correlate with performance in two inhibitory control tasks—a NoGo signal task and an emotional appraisal task [Tabibnia et al., 2011]. The present results are consistent with these prefrontal-striatal interactions showing an inverse relationship on the level of the individual time-series data between the two structures and showing that the magnitude of the interactions between the two precedes the subsequent selection with greater PFC activity preceding successful inhibitions. This would appear to fit in with the hypothesized antagonistic dual system underlying impulsive behavior, whereby an

impulsive and a reflective system interact with one another in terms of motivation and regulation of behavior—with bilateral VS encompassing the impulsive system and the rIFG the reflective system in this task.

At an anatomical level we were able to dissociate medial and lateral areas of the rIFG (Fig. 4), with the former correlating with subcortical regions in advance of the target/NoGo signal and the latter active at the timepoint of successful inhibition and not displaying any functional connections with the VS. Heterogeneity of function within inferior frontal cortex has previously been demonstrated. Chikazoe et al. [2009] used an altered go/no-go task to illustrate that while the rIFG was linked to response inhibition, a more dorsal portion—the right inferior frontal junction—was activated during the processing of infrequent stimuli. Verbruggen et al. [2010] also identified a similar functional segregation within the right inferior frontal cortex by use of a brief repetitive form of transcranial magnetic stimulation. Cai and Leung [2011] reported that subdivisions within the right inferior frontal cortex appeared to serve separate cognitive functions including triggering the response inhibition process, infrequent target detection, and rule retrieval but not inhibition of a motor response per se. This conclusion was based on the failure to find differences in rIFG between successful and unsuccessful efforts to inhibit. However, it should be noted that the temporal dimension of the brain’s response may be key—a similar amplitude of activity in the rIFG may be observed on error trials if that activity is too late to countermand the Go response [Garavan et al., 2002]. Similarly, our results indicate that subregions in this area are linked to particular cognitive functions, but this includes the successful countermanding of a motor response. That activation in the more medial rIFG region was not active at the timepoint of successful response inhibitions suggests that its frontostriatal functional connectivity appears to be involved in moderating inhibitory control over impulsive choice selection.

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