Segregating domain-general from emotional context-specific inhibitory control systems - ventral striatum and orbitofrontal cortex serve as emotion-cognition integration hubs

Qian Zhuang[a], Lei Xu[a], Feng Zhou[a], Shuxia Yao[a], Xiaoxiao Zheng[a], Xinqi Zhou[a], Jialin Li[a], Xiaolei Xu[a], Meina Fu[a], Keshuang Li[a], Deniz Vatansever[b], Keith M. Kendrick[a,b,*], Benjamin Becker[a,*]

[a] The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Laboratory for Neuroinformation, Center for Information in Medicine, University of Electronic Science and Technology of China, Chengdu, China

[b] Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, China

*Corresponding authors: Benjamin Becker (ben_becker@gmx.de) and Keith M. Kendrick (k.kendrick.uestc@gmail.com)

No. 2006, Xiyuan Ave., West Hi-Tech Zone, Chengdu, Sichuan 611731, China.

Phone: +86-28-61830811; Fax: +86-28-61830811

1

Abstract

Inhibitory control hierarchically regulates cognitive and emotional systems in the service of adaptive goal-directed behavior across changing task demands and environments. While previous studies convergently determined the contribution of prefrontal-striatal systems to general inhibitory control, findings on the specific circuits that mediate the context-specific impact of inhibitory control remained inconclusive. Against this background we employed an evaluated emotional Go/No Go task with fMRI in a large cohort of subjects (N = 250) to segregate brain systems and circuits that mediate domain-general from emotion-specific inhibition control. Particularly during a positive emotional context, behavioral results showed a lower accuracy for No Go trials and a faster response time for Go trials. While the dorsal striatum and lateral frontal regions were involved in inhibitory control irrespective of emotional context, activity in the ventral striatum (VS) and medial orbitofrontal cortex (mOFC) varied as a function of emotional context. On the voxel-wise network level, limbic and striatal systems generally exhibited highest changes in global brain connectivity during inhibitory control, while global brain connectivity of the left mOFC was less suppressed during emotional contexts. Functional connectivity analyses moreover revealed that negative coupling between the VS with inferior frontal gyrus (IFG)/insula and mOFC varied as a function of emotional context. Together these findings indicated separable domain general systems as well emotional context-specific inhibitory brain systems which specifically encompass the VS and its connections with frontal regions.

Keywords: Inhibition, Emotion, emotional Go/No Go, striatum, prefrontal cortex, domain-general

1. Introduction

Cognitive control refers to the hierarchical regulation of other cognitive and emotional systems in the service of adaptive goal-directed behavior. The inhibition of habitual or prepotent behavioral responses represents a cardinal cognitive control domain and is essential for adaptive regulation of behavior across changing task demands and environments. Performance in this domain is influenced by personal and contextual factors. Response inhibition has been associated with traits such as impulsivity (Dalley and Robbins, 2017) and deficient response inhibition has been reported across major psychiatric disorders, including drug addiction (Courtney et al., 2013; Lüscher et al., 2020), depression (Diener et al., 2012; Liu et al., 2020; Wessa et al., 2007), schizophrenia (Ursu et al., 2011; Vercammen et al., 2012) and attention deficit/hyperactivity spectrum disorders (ADHD, Karalunas et al., 2020). Response inhibition is also modulated by the emotional context, as revealed by a growing number of behavioral findings using affectively charged task stimuli in Go/No Go paradigms (Albert et al., 2012; Drevets and Raichle, 1998; Hare et al., 2005; Putman et al., 2010). A number of studies reported longer reaction times for negative stimuli and more commission errors (failed suppression of the response) for positive stimuli (Albert et al., 2012; Hare et al., 2005; Putman et al., 2010; Schulz et al., 2007), while others reported no modulatory effects (Albert et al., 2010; Brown et al., 2012).

Animal models and human neuroimaging studies have provided convergent evidence for a pivotal role of the striatum and regulatory frontal regions in response

inhibition and suggest that their functional interplay may be critical for adaptive inhibition (Hu et al., 2019; Lüscher et al., 2020; Morein-Zamir and Robbins, 2015; Volkow et al., 2011). Across species the underlying neural systems have been mapped primarily in the domain of motor-response inhibition by employing the Go/No Go paradigm that assesses the suppression of a prepotent motor response before its initiation and the stop-signal reaction time task (SSRT) that measures suppression after the motor response has been initiated. Animal models that focused on the specific contribution of striatal subregions indicate that the inhibition of prepotent motor responses is mediated by the dorsal striatal systems (Eagle et al., 2008, 2011; Eagle and Baunez, 2010) and human neuroimaging studies employing translational paradigms confirm the role of the dorsal striatum (DS) in motor inhibition (Ghahremani et al., 2012; Kelly et al., 2004; Robertson et al., 2015) while additionally emphasizing the contribution of the anterior cingulate and lateral prefrontal regions, particularly the inferior frontal gyrus (IFG) (Aron et al., 2004; Brown et al., 2012; Cromheeke and Mueller, 2014; Meffert et al., 2016; Shafritz et al., 2006; Swick et al., 2008). With respect to differentiating specific regions and circuits that mediate the influence of emotional context on response inhibition animal models are currently lacking and previous neuroimaging studies in humans revealed inconsistent results. Whereas a number of neuroimaging studies reported emotional context-specific recruitment of different regions including the striatal, amygdala-hippocampal and medial orbitofrontal regions during inhibitory control (Berkman et al., 2009;

4

Goldstein et al., 2007; Hare et al., 2005; Protopopescu et al., 2005; Roberts et al., 2013; Somerville et al., 2011; Todd et al., 2012; Torrisi et al., 2016; Wessa et al., 2007; Zhang et al., 2016), subsequent meta-analyses have revealed rather inconclusive results, with emotional context-dependent recruitment of the anterior cingulate and precuneus (Cromheeke and Mueller, 2014), the amygdala (Hung et al., 2018) or a domain-general fronto-parietal network for emotional and cognitive control being reported (Chen et al., 2018; Xu et al., 2016). These diverging findings with respect to specific brain regions and circuits mediating the influence of emotional context on inhibitory control may be (partly) explained by the comparably low sample size or the use of a priori defined regions of interest in the original studies as well as the varying selection criteria for paradigm classes in the meta-analyses.

To separate brain regions and circuits that specifically mediate domain-general and emotional context-specific cognitive control the present study employed a validated emotional linguistic Go/No Go fMRI paradigm during which a large cohort of healthy subjects (N = 250) were required to inhibit prepotent motor responses in neutral, positive and negative contexts. In addition to task-based activation changes accumulating evidence highlights the contribution of network-level interactions during distinct cognitive functions such as working memory (Vatansever et al., 2015, 2017) or response inhibition (Tsvetanov et al., 2018). To facilitate a hypothesis-free determination of the corresponding network-level mechanism that underlies domain-general versus emotional-context specific cognitive control a data-driven network-

level approach (intrinsic connectivity contrast, ICC) was employed that operates on the voxel-level and independent of pre-specified regions of interest. We initially validated the modulatory influence on the behavioral level and in line with previous studies expected that subjects would tend to exhibit longer reaction times for negative stimuli and make more errors during the suppression of responses during positive stimuli (Albert et al., 2012; Hare et al., 2005; Liu et al., 2020; Putman et al., 2010; Schulz et al., 2007). Based on previous animal models and human neuroimaging studies we expected that dorsal striatal and lateral prefrontal regions would exhibit a general engagement during inhibitory control, while regions engaged in emotional and valence processing, specifically the amygdala, ventral striatum and orbitofrontal regions (Goldstein et al., 2007; Hare et al., 2005; Taylor et al., 2018) would exhibit emotional context-specific engagement during inhibitory control. Given the pivotal role of the fronto-striatal cicruits in inhibitory control and their sensitivity to emotional context (Chang et al., 2020; Christakou et al., 2004; Li and Sinha, 2008; Somerville et al., 2011), we further hypothesized that core regions of this circuitry would exhibit emotional context-sensitive modulations on the network level.

2. Materials and Methods

2.1 Participants

N = 250 healthy, right-handed Chinese students were enrolled in the present study after providing written informed consent. Exclusion criteria included: (1) past or

6

current psychiatric or neurological disorder, and (2) regular or current use of licit and illicit drugs or medication. Data from n = 11 subjects were lost due to technical failure (n = 5, MRI system failure, n = 6, failure of the behavioral data acquisition system). Data from n = 12 subjects were excluded due to excessive head motion during MRI acquisition (>2.5mm or 2.5 degrees). A total of n = 227 subjects were included in the final behavioral and fMRI analyses (112 males; age: mean ± SD = 21.62 ± 2.32 years). The study was approved by the local ethics committee and in accordance with the latest revision of the Declaration of Helsinki.

2.2 Emotional Go/No Go fMRI Paradigm

Cognitive control and the emotional modulation of cognitive control was examined by means of a modified version of a previously validated mixed event-related block design emotional (linguistic) Go/No Go paradigm (Goldstein et al., 2007; Protopopescu et al., 2005). Briefly, the paradigm uses orthographical cues to indicate the required behavioral response. Participants were instructed to silently read words and to respond as quickly and accurately as they can to the font of the word. For stimuli presented in the normal front (Go trials), participants were required to respond via right index finger button-press but to inhibit their response to words presented in italicized front (No Go trials). Instruction was presented for 1400ms before each block. Emotional context was modulated by presenting neutral, positive and negative stimuli. The stimuli consisted of 18 neutral, 18 negative and 18 positive words written in Chinese and were matched for length (length = 4) and word frequency. An

7

independent sample of n = 18 subjects rated the emotional category (yes or no), intensity (1-9 scale), and imaginability (1-9 scale) of the word stimuli before the start of the study (details see **Supplementary Table S1**). The paradigm encompassed 24 blocks that were presented in 2 runs with 12 blocks each. Each run comprised two blocks of the six permutations of the response (Go, No Go) and emotion (positive, negative, neutral) conditions: neutral Go (neu Go), neutral No Go (neu No Go), negative Go (neg Go), negative No Go (neg No Go), positive Go (pos Go), positive No Go (pos No Go). During each go block, 18 words in normal font (100% Go trials) were presented while during no-go blocks 12 normal font words (66.7% Go trials) and 6 italicized font words (33.3% No Go trials) were presented.

Stimuli were presented for 300ms, followed by an inter-stimulus-interval (ITI) of 900ms, leading to a block duration of 21.6s. Blocks were interspersed by a low-level inter-block period of 16s. The blocks and trials were presented in pseudo-random and counter-balanced order (same block or trial never presented in succession). Total duration of the paradigm was approx. 16 minutes (**Figure 1**).
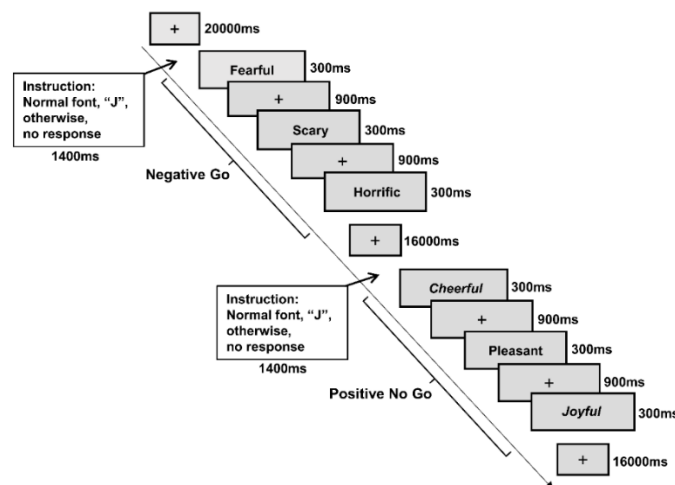
Figure 1. Experimental paradigm and timing. A negative Go block and positive No Go block are depicted for the emotional linguistic Go/No Go task.

2.3 Behavioral Data Analysis

Accuracy and response times (in Go trials) served as indices to examine the effect of inhibitory control and emotional context on the behavioral level and were examined by means of repeated measures ANOVA models. For accuracy, a two-way repeated-measures ANOVA with inhibition (Go vs. No Go) and emotion (negative vs. neutral vs. positive) as within-subject factors was employed. For response time in Go trials (correct trials), a one-way repeated measures ANOVA with the different emotional contexts was performed (negative vs. neutral vs. positive). For all behavioral analyses appropriate Bonferroni corrections were employed to account for multiple comparisons.

2.4 MRI Data Acquisition

MRI data were collected using a 3 Tesla, GE Discovery MR750 system (General Electric Medical System, Milwaukee, WI). For each subject, 488 volumes of T2*-weighted echo planar images were obtained using the following acquisition parameters: repetition time, 2000ms; echo time, 30 ms; slices, 39; slice-thickness, 3.4mm; gap, 0.6mm; field of view, 240×240 mm^2; matrix size, 64×64; flip angle, 90°. To improve normalization of the functional images high-resolution whole brain T1-weighted images were acquired (spoiled gradient echo pulse sequence with oblique acquisition, acquisition parameters: repetition time, 6ms; echo time,

9

minimum; flip angle, 9°; field of view =256 × 256mm; acquisition matrix, 256 × 256; thickness, 1mm; 156 slices). OptoActive MRI headphones (http://www.optoacoustics.com/) were used to reduce acoustic noise exposure during scanning.

2.5 MRI Data Analysis

2.5.1 fMRI Data Preprocessing

MRI data were analyzed using SPM12 software (Wellcome Trust Center of Neuroimaging, University College London, London, United Kingdom). The first 10 volumes were excluded to allow active noise canceling and to gain magnet-steady data. The remaining time-series were slice timing corrected, realigned to correct for head movement and co-registered to the T1-weighted structural images. For normalization the T1-weighted images were segmented and the corresponding transformation matrices were applied to normalize the functional time-series to Montreal Neurological Institute (MNI) standard space. Normalized data were resampled to 3mm^3 and smoothed using a Gaussian kernel with full-width at half-maximum (FWHM) of 8mm.

2.5.2 BOLD Level Analysis

The first level analyses employed an event-related analysis approaches as implemented in the general linear model. Six condition-specific regressors (neu Go, neu No Go, neg Go, neg No Go, pos Go, pos No Go) were modelled on the first level and convolved with the standard hemodynamic response function (HRF). The six

head-motion parameters were included as nuisance regressors to further control for movement-related artifacts. Contrast images of interest (all No Go > all GO, neu No Go > neu Go, neg No Go > neg Go, pos No Go > pos Go, No Go > Go) were created on the individual level. To examine general cognitive control networks and the modulation by emotional context, the following second level model were computed: (1) a one sample t test on all No Go > Go contrasts, corresponding to a main effect of emotion-unspecific inhibition, and (2) one-way repeated measures ANOVA including the emotion-specific contrasts of interest (neu No Go > neu Go, neg No Go > neg Go, pos No Go > pos Go), corresponding to an inhibition x emotional context interaction effect.

2.5.3 Functional Connectivity Analysis (Intrinsic Connectivity Contrast)

To determine connectivity profiles during inhibitory control and their modulation by emotional context an intrinsic connectivity contrast (ICC) analysis was implemented. Initially, a strict noise regression was conducted for the preprocessed data using the SPM12-based Conn functional connectivity toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012) to remove noise from white matter, cerebrospinal fluid, six head-motion parameters and the second-order derivatives. In addition, a linear detrending and a temporal band-pass filter of 0.008 Hz - inferior was applied.

Next, six condition-specific regressors (neu Go, neu No Go, neg Go, neg No Go, pos Go, pos No Go) were modelled and voxel-based global connectivity (ICC maps) were calculated on each condition for each participant. The strength of the

11

connectivity of each voxel was determined by the average r^2 value (Martuzzi et al., 2011). The main effect of inhibition and inhibition x emotion interaction effects were determined using identical second-level models as employed for the activation analysis.

2.5.4 Follow-up seed-to-whole brain connectivity analyses

To further determine the specific pathways involved in the emotional modulation of inhibitory control seed-to-voxel wise context-dependent functional connectivity analyses were computed using gPPI (gPPI) (McLaren et al., 2012). Given the hypothesized role of the striatal-frontal circuits in the emotional modulation of inhibitory control (Chang et al., 2020; Li and Sinha, 2008; Somerville et al., 2011), the analyses focused on identified regions within this circuitry. Specifically, for the follow-up functional connectivity analyses seeds (4-mm spheres) were placed at the peak coordinates of the inhibition x emotion interaction effects from the BOLD level (ventral striatum) and ICC analysis (mOFC). Main effects of inhibition and inhibition x emotion interaction effects were examined using one sample t-tests (contrast: No Go > Go) and one-way ANOVAs (contrasts: neu No Go > neu Go, neg No Go > neg Go, pos No Go > pos Go).

2.5.5 Thresholding and regions of interest

The main aim of the BOLD level analyses was to segregate regions exhibiting a general involvement in inhibitory control from regions that exhibit an emotional modulation. To facilitate a clear separation a conservative peak-level threshold was

applied on the whole brain level (p < 0.05 family-wise error, FWE) and only clusters > 10 voxels are reported. To allow a more sensitive examination on the network level a cluster-level correction approach was applied for the whole-brain ICC and functional connectivity analyses (p < 0.05 FWE, cluster level correction, initial cluster defining threshold of p < 0.001). The striatum-focused analysis for the ICC follow-up functional connectivity analyses aimed at determining the specific regions that exhibit an emotional modulation within the striatum and thus employed a small volume correction approach using a mask encompassing the entire striatum based on the Human Brainnetome Atlas (Fan et al., 2016) in combination with peak-level FWE corrected at p < 0.05. To further disentangle the direction of the emotion-specific effects, parameter estimates were extracted from 4-mm spheres centered on the peak voxels of significant interaction effects and subjected to post-hoc analyses.

3. Results

3.1 Behavioral Results

To examine the effect of emotional context on inhibitory control at the behavioral level, the repeated-measures ANOVA on the accuracy data revealed significant main effects of inhibition and emotional context as well as a significant inhibition x emotion interaction effect. Examination of the significant main effect of inhibition $(F(1, 226) = 747.84, p < 0.001, \eta_p^2 = 0.77)$, revealed a higher accuracy for Go as compared to No Go trials (Go trials: mean $\pm$ SD = 98.54% $\pm$ 3.11%, No Go trials:

13

mean ± SD = 70.81% ± 16.19%, Cohen's d = 2.38). Examining the significant main

effect of emotion ($F(2, 452) = 6.64$, $p = 0.002$, $\eta_p^2 = 0.029$) revealed a generally lower

accuracy in the positive condition compared to both, the negative (positive: mean ±

SD = 83.89% ± 10.08%, negative: mean ± SD = 85.24% ± 9.26%, $p = 0.004$, Cohen's

d = 0.14) as well as neutral condition (positive: mean ± SD = 83.89% ± 10.08%,

neutral: mean ± SD = 84.90% ± 8.89%, $p = 0.026$, Cohen's d = 0.11). Post-hoc

analyses of the significant interaction effect ($F(2, 452) = 4.22$, $p = 0.016$, $\eta_p^2 = 0.018$)

demonstrated that for No Go trials accuracy was significantly lower in the positive

condition compared to both the negative (positive: mean ± SD = 69.40% ± 18.43%,

negative: mean ± SD = 71.81% ± 17.36%, $p = 0.01$, Cohen's d = 0.13) and neutral

condition (positive: mean ± SD = 69.40% ± 18.43%, neutral: mean ± SD = 71.24% ±

16.54%, $p = 0.046$, Cohen's d = 0.11, **Figure 2A**).

For response times on Go trials, one-way repeated measures ANOVA revealed a

main effect of emotion ($F(2, 452) = 10.76$, $p < 0.001$, $\eta_p^2 = 0.045$) with post-hoc tests

demonstrating faster response times during the positive condition compared to both,

the negative (positive: mean ± SD = 316.45 ± 55.95, negative: mean ± SD = 321.49 ±

58.43, $p < 0.001$, Cohen's d = 0.09) as well as neutral condition (positive: mean ± SD

= 316.45 ± 55.95, neutral: mean ± SD = 318.93 ± 57.60, $p = 0.038$, Cohen's d = 0.04,
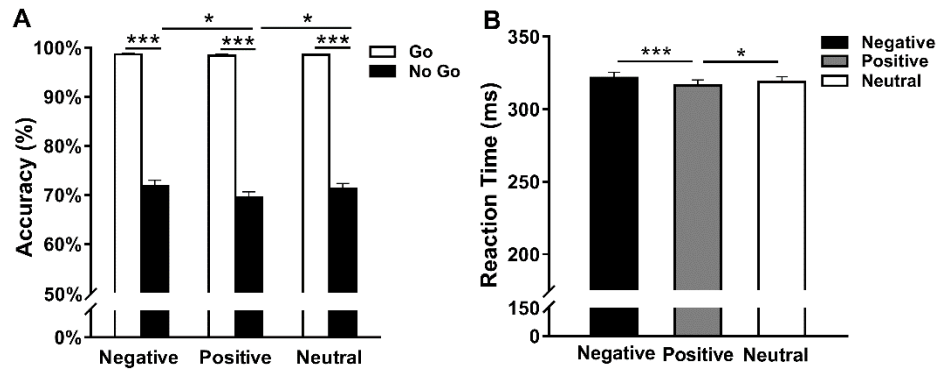
Figure 2B).

14

Figure 2. Response accuracy and reaction time in different emotional contexts. (A) Accuracy for Go trials and No Go trials across different emotional conditions. (B) Reaction time for Go correct trials across different emotional conditions. Bar graphs show mean ± SEM. * and *** denote significant post-hoc difference at $p_{Bonferroni} < 0.05$ and $p_{Bonferroni} < 0.001$ respectively.

3.2 fMRI Results

3.2.1 BOLD Level Analysis

Examining the inhibitory control networks across emotional contexts (contrasts: No Go > Go) revealed widespread activity in fronto-parietal regions, primarily in the dorsolateral prefrontal (DLPFC), inferior lateral frontal and anterior insular (AI) cortex and superior parietal regions as well as striatal, primarily dorsal striatal regions (**Figure 3A and Table 1**). The whole-brain ANOVA examining the emotional modulation of inhibition (contrasts: neu No Go > neu Go, neg No Go > neg Go, pos No Go > pos Go) revealed a significant interaction effect mainly located in the bilateral posterior IFG/anterior insula (AI) (left, Z = 6.13, $p_{FWE} < 0.001$, x/y/z: -39/15/-12; right, Z = 7.45, $p_{FWE} < 0.001$, x/y/z: 51/18/-3) as well as mOFC (left, Z = Inf, $p_{FWE} < 0.001$, x/y/z: -15/33/-15; right, Z = Inf, $p_{FWE} < 0.001$, x/y/z: 15/33/-12) and striatal regions, with additional clusters located in temporal, occipital, parietal, frontal

15

and thalamic regions (details see **Supplementary Table S2 and Figure 3B**). Notably, in contrast to the main effect that mainly engaged the dorsal striatum the interaction effect was primarily located in bilateral ventral striatum (left, $Z = 6.04$, $p_{FWE} = 0.002$, voxels = 38, x/y/z: -12/18/-9; right, $Z = 5.79$, $p_{FWE} = 0.004$, voxels = 47, x/y/z: 12/24/-6) and examining the overlap between the activity maps indicated that the VS and the mOFC were specifically recruited when emotional context was accounted for (**Figure 3C**). Post-hoc examination of the extracted parameter estimates revealed that activation in the posterior IFG/AI increased less during inhibition in the positive context compared to both, neutral and negative contexts (negative, left IFG/AI: $p < 0.001$; right IFG/AI: $p = 0.033$; neutral, left IFG/AI: $t(226) = 5.89$, $p < 0.001$; right IFG/AI: $t(226) = 8.46$, $p < 0.001$), whereas activation in the bilateral VS and mOFC was significantly suppressed in the neutral context as compared to both positive and negative context (positive, left VS: $p < 0.001$; right VS: $p < 0.001$; left mOFC: $p < 0.001$; right mOFC: $p < 0.001$; negative, left VS: $p < 0.001$; right VS: $p < 0.001$; left mOFC: $p < 0.001$; right mOFC: $p < 0.001$, **Figure 3D**).
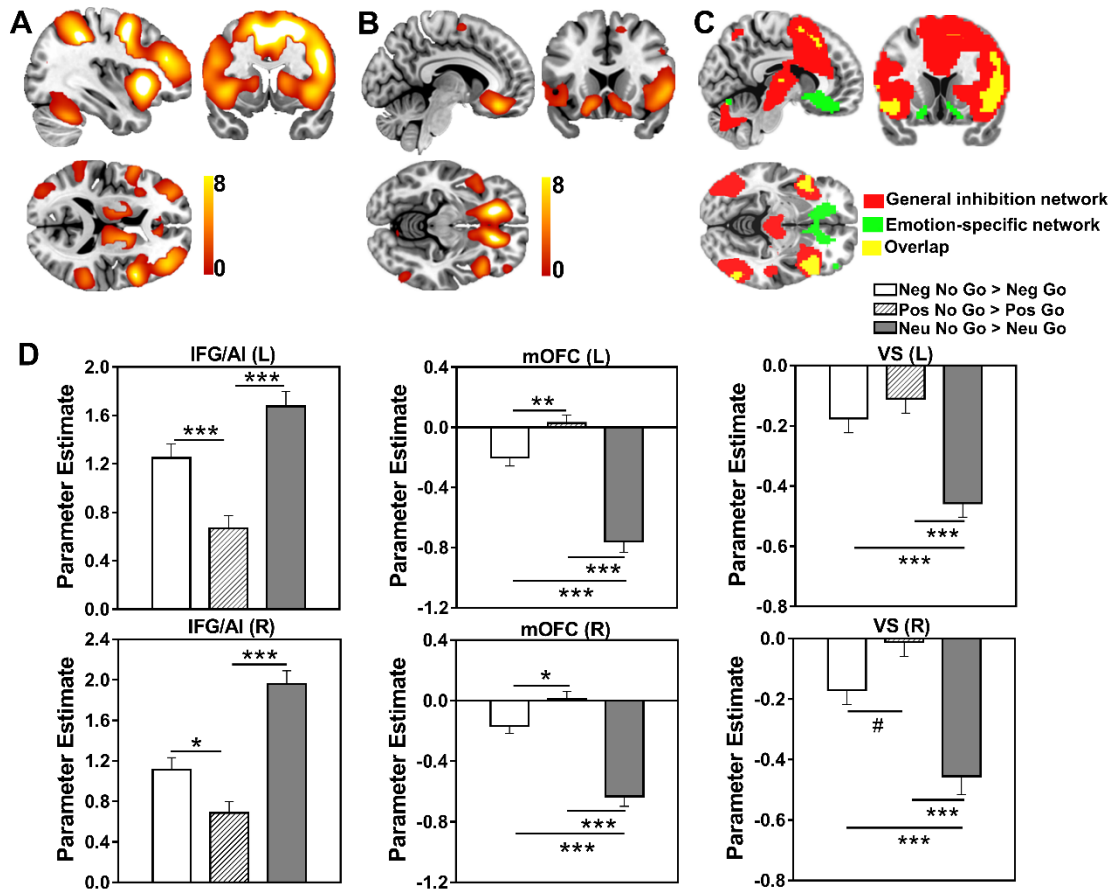
16

Figure 3. Brain activation patterns during general inhibition and interactions with emotional context. (A) General Go/No Go inhibitory network on whole brain level. (B) Activations from the interaction effect of inhibition and emotional context (contrasts: neu No Go > neu Go, neg No Go > neg Go, pos No Go > pos Go) on whole brain level. (C) Distribution in general Go/No Go inhibitory network and emotion-inhibition interaction network and (D) corresponding bar graphs based on extracted parameter estimates for the activated regions of interest (left IFG/AI and right IFG/AI, left mOFC and right mOFC, left VS and right VS). Bar graphs show mean ± SEM. #, * and *** denote significant post-hoc difference at $p < 0.05$, $p_{Bonferroni} < 0.05$ and $p_{Bonferroni} < 0.001$ respectively.

Table 1. Brain regions showing general Go/No Go network on whole brain level

Regions	Cluster K	Coordinates			t value
		X	Y	Z	

Frontal lobe extending to parietal, temporal lobe	19467	18	6	57	25.27
		27	3	51	25.13
		-3	12	45	24.53
R antOFC	74	27	45	-21	9.03
L Calcarine	146	-12	-75	9	8.30
R Calcarine	53	15	-72	9	6.53
L Ventral Striatum	12	-9	6	6	7.60
		-15	6	-3	6.72
R Ventral Striatum	51	18	6	-3	10.15
		12	12	3	9.85
		9	3	3	8.07
L Dorsal Striatum	148	-27	12	6	14.15
		-30	9	-6	9.09
		-12	0	12	11.42
R Dorsal Striatum	221	27	15	3	14.52
		15	-3	15	13.77
		15	6	12	13.03

Note: All clusters passed the threshold at peak level $p_{FWE} < 0.05$, cluster size $k > 10$.

FWE, familywise error; L, left; antOFC, anterior orbital frontal cortex; R, right.

3.2.2 Follow-up functional connectivity analysis

To further determine networks that couple in a general versus emotion-specific fashion with the identified VS regions a follow-up seed-to-voxel connectivity analysis with the left and right VS as determined by the BOLD level analysis was conducted. The left VS exhibited general negative association with fronto-parietal, temporal and limbic regions during inhibition (contrasts: No Go > Go, **Figure 4A** and **Table 2**), while the examination of the interaction between emotion and inhibition (contrasts:

neu No Go > neu Go, neg No Go > neg Go, pos No Go > pos Go) revealed interactive effects on left VS coupling with the right IFG/insula (right IFG/insula, Z = 4.49, p_{FWE} < 0.001, x/y/z: 30/27/3, **Figure 4B**). Post-hoc analyses on the extracted parameter estimates revealed that left VS connectivity with right IFG/insula was significantly decreased in the positive compared to the negative context (right IFG/insula: p = 0.016) and further decreased in the neutral context (right IFG/insula: p = 0.005, **Figure 4B**).
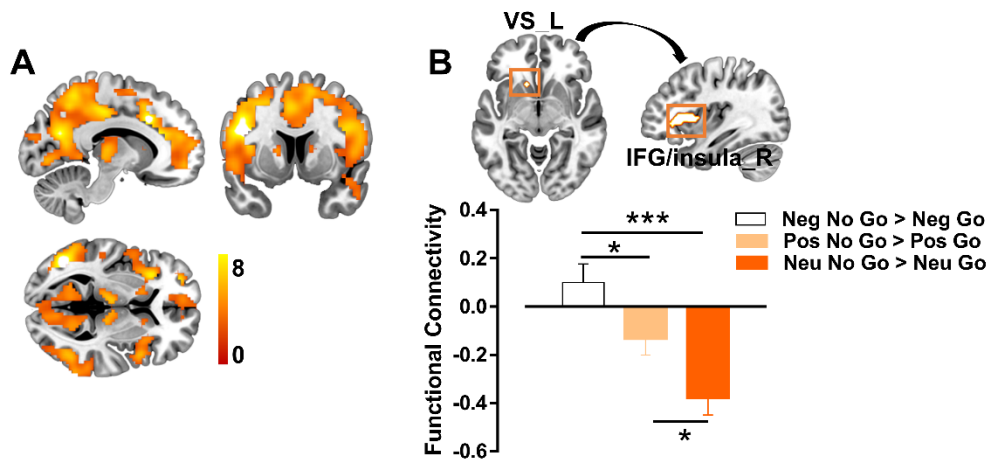

Figure 4. Domain-general and emotion specific functional connectivity with ventral striatum as seed. (A) Brain regions showing significant activations in No Go vs Go conditions on connectivity level. (B) Activations from the interaction effect of inhibition and emotional context (contrasts: neu No Go > neu Go, neg No Go > neg Go, pos No Go > pos Go) on connectivity level and corresponding bar graphs show functional connectivity between left VS and right IFG/insula. Bar graphs show mean ± SEM. * and *** denote significant post-hoc difference at $p_{Bonferroni}$ < 0.05 and at $p_{Bonferroni}$ < 0.001 respectively.

Table 2. Brain regions showing significant activations in No Go vs Go conditions on connectivity level

Regions	Cluster K	Coordinates			t value
		X	Y	Z	
Frontal lobe extending	18746	-21	39	24	8.05
to parietal lobe		-6	18	36	7.00
		-39	9	21	6.79

Note: All clusters passed the threshold at cluster level $p_{FWE} < 0.05$. FWE, familywise

error.

3.2.3 ICC Analysis

Examining the general inhibitory control networks (contrasts: No Go > Go) revealed a

widespread network of increased whole brain connectivity during inhibition

encompassing nearly the entire dorsal and ventral striatum as well as the limbic lobe

with additional clusters located in the cerebellum, middle cingulate cortex (MCC) and

fronto-temporal regions (**Figure 5A** and **Table 3**). Examination of the modulatory

influence of emotional context revealed significant interaction effects in the left

mOFC ($Z = 3.71$, $p_{FWE} = 0.002$, x/y/z: -18/21/-15, **Figure 5B**) and additional parietal

regions (**Supplementary Table S3**) on the whole brain level. Post-hoc analyses of the

extracted parameter estimates revealed that connectivity of the left mOFC

significantly decreased in the neutral context during inhibition compared to both

negative and positive contexts (negative, left mOFC: $p < 0.001$; positive, left mOFC:

$p < 0.001$, **Figure 5B**), reflecting a valence-independent emotional modulation in this
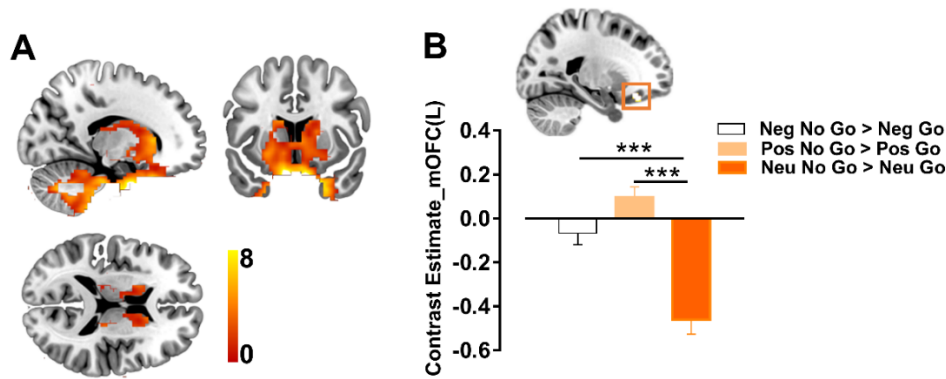
region.

Figure 5. Brain regions showed global brain connectivity in general inhibition and emotion specific inhibition. (A) Brain regions showing global brain connectivity on No Go vs Go conditions from ICC analysis. (B) Emotion's modulatory effects (contrasts: neu No Go > neu Go, neg No Go > neg Go, pos No Go > pos Go) showed higher changes of left mOFC in global brain connectivity and corresponding bar graphs based on extracted parameter estimates. Bar graphs show mean ± SEM. *** denote significant post-hoc difference at $p_{Bonferroni} < 0.001$.

Table 3. Brain regions showing global brain connectivity on No Go vs Go conditions from ICC analysis

Regions	Cluster K	Coordinates			t value
		X	Y	Z	
Limbic lobe extending to	9774	-6	9	-27	13.91
cerebellum, temporal,		-15	-9	-45	13.20
frontal lobe		51	-39	-30	12.87
R MCC extending to	155	15	-12	48	8.10
SMA		9	-21	57	5.08
		15	24	30	5.47
R Postcentral gyrus	40	48	-6	30	4.55
		42	-15	33	4.32
		48	-6	18	4.08
L Paracentral lobule	102	-9	-21	60	5.18

Region	Size	x	y	z	t
		-9	-24	51	5.00
L Dorsal Striatum	262	-12	12	18	7.52
		-24	12	-9	7.06
		-18	-15	24	7.02
R Dorsal Striatum	263	18	21	6	8.94
		12	15	18	8.56
		30	-6	12	5.42
L Ventral Striatum	202	-15	0	-9	8.91
		-9	6	-15	7.37
		-21	9	-9	6.98
R Ventral Striatum	196	18	21	3	8.12
		12	18	-6	7.10
		6	9	0	6.95

Note: All clusters passed the threshold at cluster level $p_{FWE} < 0.05$. FWE, familywise error; L, left; MCC, middle cingulum cortex; MTG, middle temporal gyrus; R, right; SFG, superior frontal gyrus; SMA, supplementary motor area.

3.2.4 Follow-up Functional Connectivity Analysis

To further determine the specific fronto-striatal circuits that exhibit an emotional modulation during inhibitory control a follow-up seed-to-voxel functional connectivity analysis of the identified left mOFC region was conducted. The analysis revealed that this region exhibited a generally (emotion-unspecific, contrasts: No Go > Go) negative correlation with a widespread fronto-parietal, occipital and temporal regions during inhibition (**Figure 6A** and **Table 4**). Interaction effects of emotion on inhibition-related functional connectivity of the left mOFC were observed within the striatum (SVC corrected for the entire striatum), primarily in the left

ventral part (Z = 3.81, p_{FWE} = 0.006 SVC for the entire striatum, voxels = 22, x/y/z: -15/6/-12, **Figure 6B and Table S4**). Post-hoc analysis on extracted parameter estimates showed that mOFC connectivity with the left VS was decreased for the neutral as compared to both positive and negative contexts (positive: p = 0.004; negative: p < 0.001, **Figure 6B**).
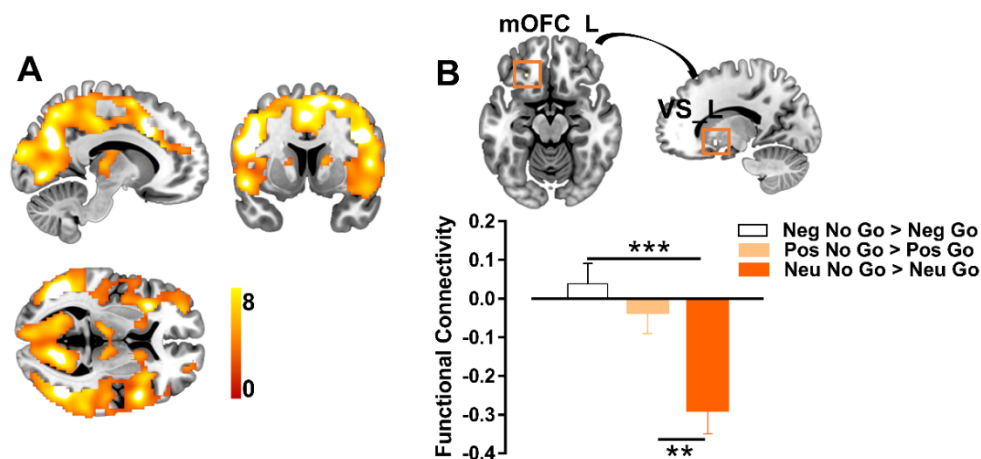

Figure 6. Domain-general and emotion specific functional connectivity with mOFC as seed. (A) Brain regions showing significant activations in No Go vs Go condition for connectivity results. (B) Activations from the interaction effect of inhibition and emotional context (contrasts: neu No Go > neu Go, neg No Go > neg Go, pos No Go > pos Go) on connectivity level and corresponding bar graphs show functional connectivity between left mOFC and left VS. Bar graphs show mean ± SEM, ** and *** denote significant post-hoc difference at $p_{Bonferroni}$ < 0.01 and $p_{Bonferroni}$ < 0.001 respectively.

Table 4. Brain regions showing significant activations in No Go vs Go condition on connectivity level

Regions	Cluster K	Coordinates			t value
		X	Y	Z	
Frontal lobe extending	23949	-54	-36	30	7.92

23

to parietal, occipital and	-42	-66	3	7.84
temporal lobe	6	15	42	7.83

Note: All clusters passed the threshold at cluster level $p_{FWE} < 0.05$. FWE, familywise

error

4. Discussion

The present study aimed at segregating brain systems and circuits that mediate

domain-general versus emotional context-specific inhibitory control by means of an

emotional Go/No Go paradigm with concomitant fMRI acquisition in a large sample

of healthy subjects. On the behavioral level more commission errors (No Go trials)

and faster response times (Go trials) were observed in the positive context compared

to both the negative and neutral contexts, reflecting successful emotional modulation

of inhibitory control. On the neural level, regional activity in dorsal striatal, anterior

insular and lateral frontal regions increased independent of emotional context while

inhibition-related activity in the ventral striatum, anterior insula and medial

orbitofrontal cortex varied as a function of emotional context such that the AI

exhibited increased activation, while the VS and mOFC exhibited less suppression

during inhibition in positive contexts. On the network level cerebellar, limbic and

striatal systems generally increased voxel-wise whole brain connectivity during

inhibitory control, while whole brain connectivity of the left mOFC was less

suppressed during emotional contexts. Follow-up functional connectivity analyses

24

moreover revealed that negative functional coupling between the left VS and the contralateral IFG/insula as well as the left mOFC and the ipsilateral striatum, specifically the VS, during inhibition in neutral contexts was attenuated during inhibition in both emotional contexts. Taken together, the findings indicate separable domain general as well emotional context specific inhibitory brain systems.

In line with previous studies employing emotional Go/No Go paradigms we observed higher error rates for No Go trials as compared to Go trials (Albert et al., 2010) as well as more commission errors for No Go trials in the positive context (Albert et al., 2012; Hare et al., 2005; Putman et al., 2010) as compared to both, negative and neutral contexts, reflecting successful emotional modulation of response inhibition. Together with faster response times for positive stimuli this may reflect approach tendencies for positive stimuli facilitating approach while reducing avoidance (Albert et al., 2010).

Examination of inhibition-related brain activity across emotional contexts revealed increased activity in a broad bilateral fronto-parietal cognitive control network, encompassing the lateral frontal, anterior insular, supplementary motor and superior parietal cortices, as well as striatal, particularly dorsal striatal regions. The involvement of the fronto-parietal cognitive control network is in line with previous neuroimaging studies in humans suggesting a general involvement of the fronto-parietal cognitive control network across executive domains (Chambers et al., 2009; Hung et al., 2018; Langner et al., 2018), while the engagement of primary

25

dorsal striatal regions is in line with animal models suggesting a critical role of these regions in cognitive and motor control (Eagle et al., 2008, 2011; Eagle and Baunez, 2010; Haber, 2016).

Notably, interactions between emotional context and inhibitory control specifically engaged more medial prefrontal, particularly medial orbitofrontal, and ventral regions of the striatum. While animal and human studies demonstrated a critical role of the DS in cognitive and motor inhibitory control (Eagle et al., 2010, 2011; Ghahremani et al., 2012; Robertson et al., 2015) the VS and mOFC appear not critical for response inhibition per se (Robertson et al., 2015; Stalnaker et al., 2015) but orchestrate several emotional and reward-related processes, such that previous meta-analyses of human neuroimaging studies revealed convergent activation during positive and negative valence processing, as well as reward and decision making (De La Vega et al., 2016; Diekhof and Gruber, 2010; Hiser and Koenigs, 2018; Yang et al., 2020). Examination of extracted parameter estimates revealed that both regions were suppressed during inhibitory control in neutral contexts, while suppression was attenuated or abolished in emotional contexts, suggesting that the task-irrelevant emotional information interfered with this mechanism and may reflect the involvement of the VS-mOFC system in detecting biologically significant stimuli (Cooch et al., 2015). In contrast to our hypotheses no emotional context-sensitive interactions with inhibitory control were observed in the amygdala. This is in line with previous inhibitory control studies employing emotional linguistic stimuli

26

(Goldstein et al., 2007), while other studies employing human face stimuli reported that amygdala activity varied as a function of emotional context (Hare et al., 2005). Given the pivotal role of the amygdala in social processes, including facial emotion recognition (Becker et al., 2012), the divergence may point to a specific role of the amygdala in inhibitory control in social contexts.

The second main aim of the study was to determine general and emotional-context specific changes on the network level during inhibitory control. Examination of voxel-level whole brain connectivity profiles revealed generally increased global connectivity of subcortical systems, including cerebellar, limbic and striatal, regions during inhibitory control while interactions between inhibitory control and emotional context specifically modulated connectivity profiles in the left precuneus and left mOFC, such that network level communication of these regions was suppressed during inhibitory control in neutral contexts yet less suppressed during negative or enhanced during positive contexts. While conceptual network-level approaches to inhibitory control emphasize the role of fronto-striatal cicruits in general inhibitory motor control (Alexander et al., 1986; Jahanshahi et al., 2015), more recent animal and human studies indicate that a neural network comprising mOFC and ventral striatal and limbic regions may mediate emotion inhibition interactions and reward related impulsive control (Goldstein et al., 2007; Hampton et al., 2017; Schulz et al., 2014; Wang et al., 2019).

Specifically, animal and human lesion studies have demonstrated the critical role of the mOFC in emotion processing as well as goal-directed response execution (Gourley et al., 2010; Mar et al., 2011; Noonan et al., 2010; Pujara et al., 2016; Shamay-Tsoory et al., 2003). In line with these findings, the mOFC changes during inhibitory control in emotional contexts emphasize the role of this region as an integrative hub at the intersection of emotional processes and inhibitory control.

Subsequent functional connectivity analyses of both, the VS and the mOFC region exhibiting emotional interactions in the BOLD activation or ICC analyses, respectively, suggest an important role of the ventral striatal-prefrontal communication in mediating the effects of emotional context on inhibition. Whereas both regions exhibited a generally strong negative coupling with core regions of the fronto-parietal control network, negative coupling between the VS and IFG/insula as well as mOFC and VS in neutral contexts was attenuated in positive contexts or switched to positive coupling in negative contexts.

The domain-general connectivity pattern of the VS is consistent with previous studies reporting negative connectivity of VS with fronto-parietal regions involved in inhibitory control (Behan et al., 2015; Diekhof and Gruber, 2010; Diekhof et al., 2012). Moreover, the context-independent negative coupling between mOFC with frontal parietal regions involved in executive control, is in accordance with previous findings suggesting a competing interaction between reward processing of the mOFC regions and executive control systems, including the dorsolateral PFC as well as

28

parietal regions with the strength of the competing interaction being associated with inhibitory control on the behavioral and trait level (McClure et al., 2004; Zhai et al., 2015).

In line with the BOLD activity findings specifically the VS exhibited emotional context dependent modulations. Previous animal models demonstrated that - in line with focal VS lesions – VS-prefrontal disconnections produce marked impairments in the influence of emotional context on inhibitory control (Christakou et al., 2004; Feja and Koch, 2015). Given that previous animal and human studies examining structural connection between prefrontal/insular and ventral striatal regions suggest an important role in social decision making (Chikama et al., 1997; Leong et al., 2016; Rogers-Carter et al., 2019), as well as interoceptive sensitivity and behavioral control (Jaramillo et al., 2018), enhanced PFC-VS in negative relative to positive contexts may reflect a higher salience of negative stimuli during inhibitory control.

There are several limitations in the current study. First, while only fear, happy and neutral word stimuli were used in the present study, sad or angry word stimuli were not included and whether they may have differential influence on inhibition control should be investiagted in future studies. Second, only young adults were enrolled in the present study. Given that previous studies have revelaed an age-dependent effects on inhibition control (Somerville et al., 2011), it is possible that our current findings could not extend to individuals in other age groups.

In conclusion, using a validated emotional Go/No Go task in a large cohort of subjects (N = 250) allowed us to separate brain systems and specific circuits that mediated domain-general and emotional context-specific inhibitory control. The findings suggest a specific role of the VS and its connections with mOFC and insular regions in mediating the impact of emotional context on inhibitory control. The findings moreover suggest that emotional contexts - especially positive contexts – may interfere with inhibitory control system. The findings may have moreover implications for substance addiction as well as neuropsychiatric disorders characterized by deficient inhibitory control and enhanced reward sensitivity.

Declaration of conflicting interests

The authors declared no conflicts of interest with their research, authorship or the

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33

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