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Impaired Frontal-Basal Ganglia Connectivity in Adolescents with Internet Addiction

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Understanding the neural basis of poor impulse control in Internet addiction (IA) is important for understanding the neurobiological mechanisms of this syndrome. The current study investigated how neuronal pathways implicated in response inhibition were affected in IA using a Go-Stop paradigm and functional magnetic resonance imaging (fMRI). Twenty-three control subjects aged 15.2 ± 0.5 years (mean \pm S.D.) and eighteen IA subjects aged 15.1 ± 1.4 years were studied. Effective connectivity within the response inhibition network was quantified using (stochastic) dynamic causal modeling (DCM). The results showed that the indirect frontal-basal ganglia pathway was engaged by response inhibition in healthy subjects. However, we did not detect any equivalent effective connectivity in the IA group. This suggests the IA subjects fail to recruit this pathway and inhibit unwanted actions. This study provides a clear link between Internet addiction as a behavioral disorder and aberrant connectivity in the response inhibition network.

Internet addiction (IA) is described as “problematic Internet use”^{1,2} or “pathological Internet use”³ and refers to the inability to control the use of the Internet^{2,4,5}. IA has become more prevalent over recent years. Previous studies suggest that Internet addiction is found in individuals from different areas and backgrounds^{6–10}. The prevalence of Internet addiction varies from 5.4% in Italy⁸ to 18.3% in Britain⁷. IA has been reported to lead to academic, social, and occupational impairment⁴. Furthermore, the levels of loneliness¹¹, depression^{11–13}, compulsivity¹¹ and suicide ideation^{12,14} are higher in Internet addiction relative to control subjects. In particular, problems are more commonly reported by younger and more recent Internet users¹⁵.

A significant and interesting finding is that IA is associated with poor impulse control^{2,16–20}. Individuals with IA usually use the Internet compulsively²¹, despite adverse consequences; show diminished control over Internet use, and feel a great urge to be ‘online’ when disconnected^{17,20}. An early study reported that problematic Internet use of all twenty subjects studied met DSM-IV criteria for an impulse control disorder (ICD) not otherwise specified². Similarly, Treuer and co-authors¹⁷ found that the prevalence of ICD features is high among Internet users and we have noted that adolescents with IA exhibit more impulsivity than controls¹⁸. Based on these findings, it has been argued that IA may represent a subset of ICD^{16,17}. Understanding the neural basis underlying poor impulse control in IA subjects may therefore be of great importance for the diagnosis and treatment of this disorder.

Recently, there has been increasing interest in investigating the neurobiological mechanisms of IA using neuroimaging^{19,22–30}. These studies have revealed lower gray matter density²⁶, reduced orbitofrontal cortical thickness²⁹, abnormal white matter fractional anisotropy (FA)²⁵, impaired brain activity^{19,27}, and decreased functional connectivity³⁰ in individuals with IA. In particular, studies performed by Dong and colleagues have demonstrated altered brain activity that was associated with less efficient impulse inhibition in IA subjects^{19,27}. Lower NoGo-N2 amplitude, higher NoGo-P3 amplitude, and longer NoGo-P3 peak latency were detected in the IA group during a Go/NoGo task¹⁹. In addition, significantly greater activity in the anterior and posterior cingulate cortex was found in IA subjects using event-related functional magnetic resonance imaging (fMRI)²⁷.

Convergent findings from previous studies indicate that impulsive responses are inhibited by engaging frontal-basal ganglia pathways involving the right inferior frontal gyrus (IFG)^{31–38}, the striatum^{36,38–40}, the pre-supplementary motor area (pre-SMA)^{37,41,42}, and the subthalamic nucleus (STN)^{33,43}; yet little is known about how these

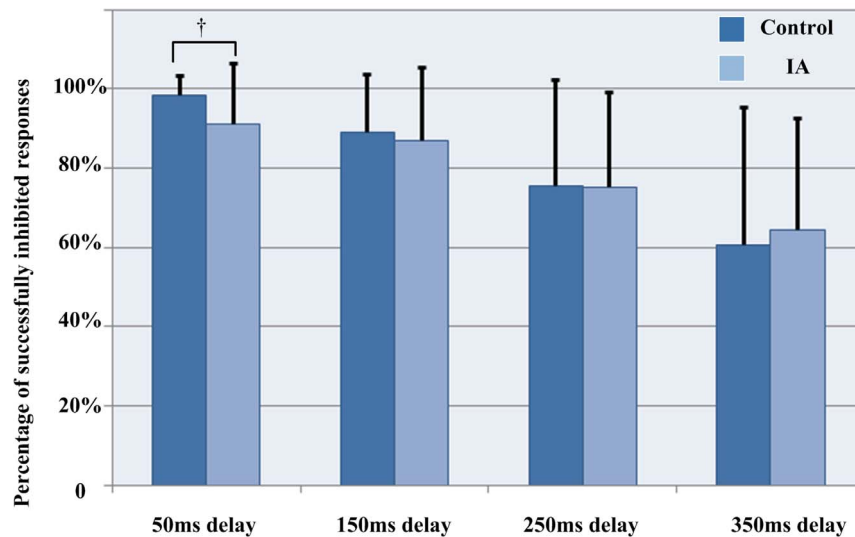


Figure 1 | The behavioral performance of the control and IA group during the Go-Stop task. The percentage of successfully inhibited responses was significantly lower in the IA group than the controls during the 50 ms delay task ($p < 0.05$). † $p < 0.05$.

response inhibition pathways are affected in IA. We used stochastic dynamic causal modeling (DCM) – a technique that measures the directed (effective) connectivity among brain regions – to characterize a network including the IFG, striatum and pre-SMA in healthy subjects and IA adolescents while performing Go-Stop task. As a behavioral measure of impulsivity, this task assesses the capacity to inhibit a response that has already been initiated. Three hypotheses were tested: 1) IA subjects would show impaired response inhibition during the Go-Stop task; 2) the frontal-basal ganglia pathways would be disrupted in IA; 3) impaired response inhibition would be associated with abnormal information flow in the frontal-basal ganglia pathways.

Results

Behavioral performance. The IA group showed impaired response inhibition during the Go-Stop task (Fig. 1). The percentage of successfully inhibited responses was significantly lower in the IA group than the controls during a 50 ms delay task ($p < 0.05$).

However, when the task became harder, both groups demonstrated difficulty withholding their response. Although the control group performed better during the 150 ms and 250 ms delay tasks, the differences did not reach significance ($p < 0.05$).

Conventional fMRI. Conventional fMRI analysis (using statistical parametric mapping) revealed that the response inhibition network, including the right IFG, the right striatum and the left pre-SMA were activated in the control group, when the subjects tried to inhibit their responses (Table 1, Fig. 2a). The right IFG and striatum survived small volume correction: $p < 0.05$, FWE corrected. In contrast, only the left superior frontal gyrus, the left and the right striatum were activated during response inhibition in the IA subjects (Table 1, Fig. 2b). Two-sample t tests (at the group level) showed that activations in bilateral IFG and the right striatum were weaker in the IA group compared to the control group (Table 1, Fig. 2c). This cluster survived correction at $p < 0.05$ for a small volume correction. On the other hand, we observed increased activation of the left superior frontal gyrus in the IA group (Table 1, Fig. 2d).

Table 1 | Brain regions that showed significant activation in the control and IA group during response inhibition

Regions	L/R	BA	Cluster size	MNI coordinates			T-value
				X	Y	Z	
Control							
Culmen	L		145	-8	-40	-20	4.68
Putamen, Insula and IFG*	R	13,45,47	615	28	2	4	5.42
IFG	L	45	509	-52	20	6	4.77
Putamen	L		23	-18	12	0	3.93
Caudate Body	L		33	-6	0	12	3.86
Angular Gyrus	L	39	206	-56	-64	34	5.71
Middle Frontal Gyrus	L	6	38	-44	0	46	4.06
SMA	R/L	6	415	10	10	60	4.88
IA							
Caudate Body	L/R		132	2	2	14	5.72
Superior Frontal Gyrus	L	9	15	-4	54	38	3.89
Control > IA							
Vermis	R		48	4	-36	-20	3.84
Insula, Putamen, and IFG*	R	13,47	71	34	14	-4	4.18
Insula and IFG	L	13	14	-44	10	2	3.64
IA > Control							
Superior Frontal Gyrus	L	9	11	-10	54	40	3.80

*indicates clusters survived small volume correction around peak coordinates as reported by Aron et al.³³; all other clusters are reported at a voxel-level significance threshold of $p < 0.001$, uncorrected.

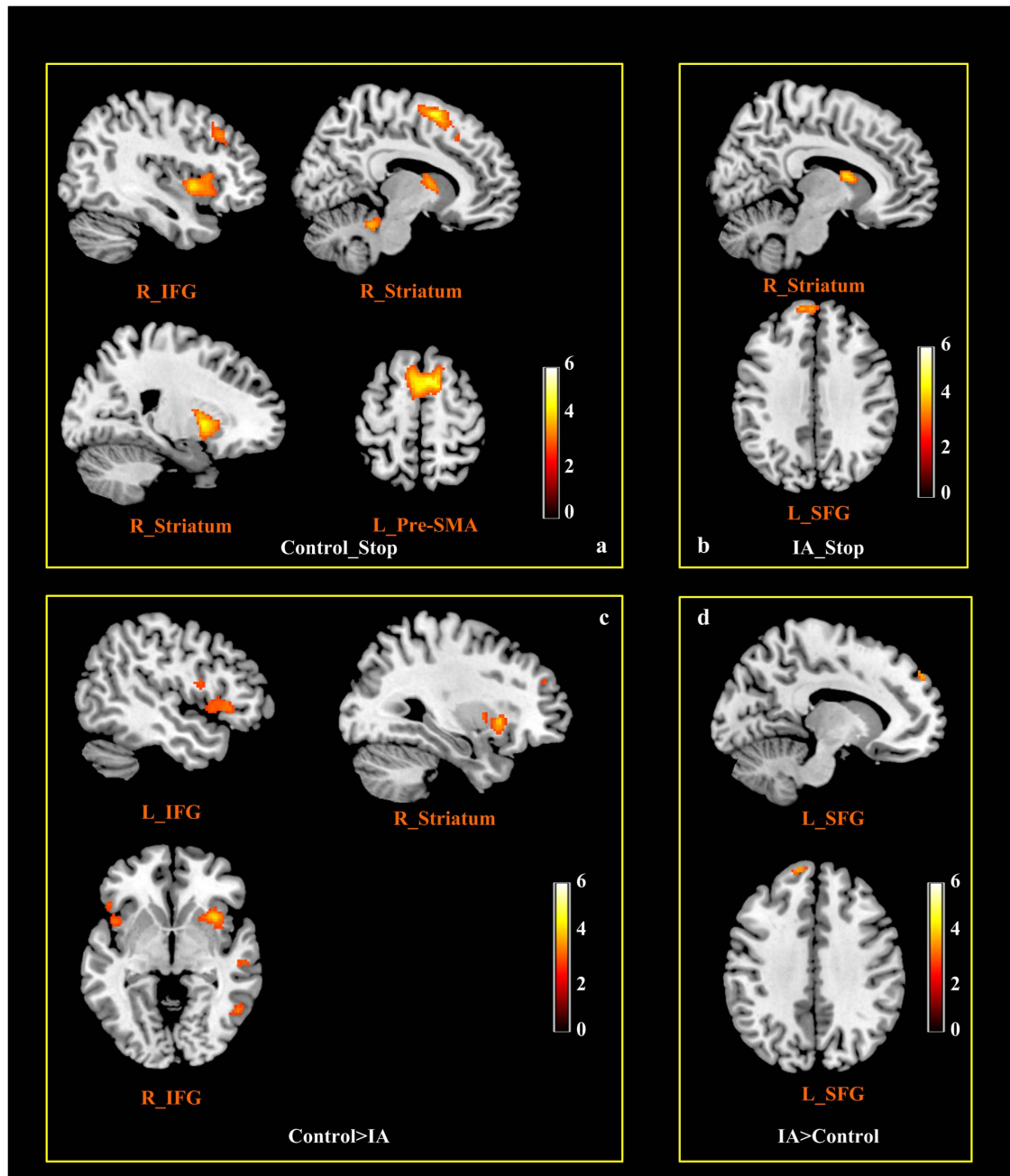


Figure 2 | Brain activation during response inhibition in the controls and the IA subjects. (a) Core regions in the response inhibition network – including the right IFG, the right striatum and bilateral pre-SMA – were activated when control subjects tried to suppress responses. (b) Only the right striatum in the response inhibition network showed a significant activation in the IA group. (c) Results from a two-sample *t*-test showed reduced activation in bilateral IFG and the right striatum in the IA group relative to controls. (d) Increased activation in the left superior frontal gyrus was detected in the IA group. These results are threshold at $p < 0.005$, uncorrected for display purposes. IFG, inferior frontal gyrus; pre-SMA, pre-supplementary motor area; SFG, superior frontal gyrus.

Effective connectivity. Significant connections at the group level (one-sample *t*-test at $p < 0.05$, Bonferroni corrected for multiple comparisons) are shown in Fig. 3. In all subjects, V2 exerted a significant positive influence on the activity of the pre-SMA. However, the connectivity between the IFG and the pre-SMA, between the pre-SMA and the striatum, and from the IFG to the striatum was only significant in the control group (Fig. 3a). Conversely, the effective connectivity from the pre-SMA to V2 was only significant in the IA group (Fig. 3b).

Finally, we calculated the correlation between behavioral performance and the strength of the connections. We found a positive correlation between the strength of the connection from the IFG to the

striatum and the percentage of successfully inhibited responses during the 150 ms and 250 ms delay tasks in all subjects. The behavioral performance was also negatively correlated with the strength of the connection from V2 to the pre-SMA, from the IFG to the pre-SMA, and from the pre-SMA to the IFG (Fig. 4). These results provide a behavioral validation of the quantitative effective connectivity estimates based purely on the fMRI data.

Discussion

The aim of the present study was to investigate how neural pathways underlying response inhibition were affected in IA using a Go-Stop

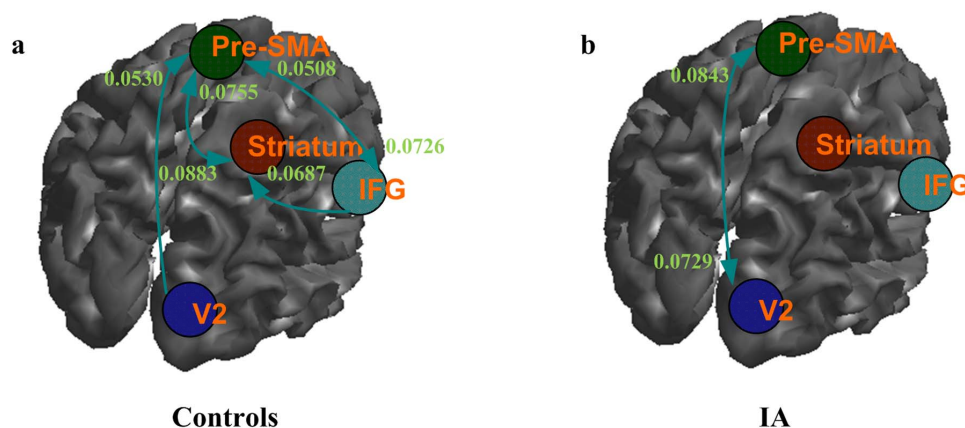


Figure 3 | Effective connectivity within the response inhibition network, in the controls and IA subjects (a) significant connectivity (at the group level) among ROIs in the control group. (b) Significant connectivity in the IA group.

paradigm. Our results showed that core brain regions in the response inhibition network – including the IFG and the striatum – exhibited stronger activation in the control group than in the IA group. Crucially, a DCM analysis revealed directed connectivity between the frontal cortex and the striatum that was consistent (significant) in control subjects. However, we did not detect any significant effective connectivity between regions in the frontal-basal ganglia pathways in the IA group. These findings suggest that abnormalities in the neural pathways in the fronto-basal ganglia system underlie behavioral response inhibition in the IA group.

In this study, we found that the percentage of successfully inhibited responses was significantly lower in the IA group, suggesting impaired response inhibition in IA adolescents. This result is in line with previous studies that reported poor impulse control in IA^{2,16–20}. Moreover, conventional fMRI analysis detected reduced activation of the bilateral IFG and the right striatum in the IA group during response inhibition. Convergent findings from human studies have suggested that the right IFG is crucial for response inhibition^{31,32,34,36,42}. Brain activations in this region have been shown to be correlated with successful inhibitory control³². Patients with lesions of the right frontal lobe needed more time to suppress a response than controls. Furthermore, IFG damage is also associated with stop signal reaction time (SSRT)³¹. Stimulation of the IFG impaired the ability to inhibit an action^{34,42}. Considering the critical role of the right IFG in response inhibition, hypoactivation of this region may account for the poor impulse control observed in our study and previous studies of IA subjects^{2,16–20}.

Neurobiologically, response inhibition has been suggested to be mediated via the indirect and the hyperdirect basal ganglia pathways^{44–46}. The hyperdirect pathway is thought to rapidly suppress a response through a projection from the frontal cortex to the STN^{44,46}. In contrast, the indirect pathway is thought to be slower, because it has more synapses than the hyperdirect pathway^{47,48}. In the indirect pathway, cortical outputs are first sent to the striatum. Neuronal signals are then passed to the globus pallidus pars externa and, finally, the STN.

Because we did not detect significant activation of the STN during response inhibition, this region was not included in our DCM – and thus we did not assess the integrity of the hyperdirect pathway. However, our results provide evidence for a key role of the indirect pathway in response inhibition. Our DCM results support the notion that when a stop signal is presented, the sensory input is relayed to the frontal cortex through a connection from V2 to the pre-SMA. The pre-SMA then communicates with the IFG via bidirectional connections. Finally, the IFG sends a stop command to the striatum to suppress the unwanted response.

The results of the DCM analysis are in line with findings from recent effective connectivity studies that also implicate the indirect

pathway in suppressing responses^{44,49}. Using a novel method (ancestral graphs), Jahfari and co-authors found that the indirect pathway between the cortex and the caudate played an important role in response inhibition. They also noted that higher connection strengths between the cortex and the caudate were associated with more efficient response inhibition⁴⁴. Findings from effective connectivity studies are supported by studies using tractography data^{35,50}. A projection between the IFG and pre-SMA is consistently reported in these studies^{35,50}. Fiber tracts connecting the striatum with the inferior frontal gyrus, pars opercularis (IFGoper) were also reported in a recent diffusion tensor imaging study⁵⁰. Transcranial magnetic stimulation (TMS) studies have shown similar results^{38,42}: stimulation of the IFG was found to increase right striatal activation, implicating the indirect pathway in reactive inhibition³⁸.

One of the main contributions of this study is the detection of aberrant effective connectivity within the response inhibition network in IA. In contrast to control subjects, consistent directed connectivity between the IFG and the pre-SMA, between the pre-SMA and the striatum, and from the IFG to the striatum were not detected in the IA group, suggesting a failure to recruit the indirect pathway to suppress unwanted actions in Internet addiction.

Our hypotheses were further verified by the association between connection strengths and subjects' performance during the Go-Stop task. Stronger IFG-striatum connections are associated with more successful response inhibition. This makes perfect sense: according to the DCM analysis, the connection strength describes the strength of a coupling in terms of the rate at which neuronal responses are elicited in the target region (in other words connection strengths are effectively rate constants in 1/s, Hz)⁵¹. Thus a larger connection strength suggests a faster effect on the target region, resulting in more efficient termination of the action. In contrast, lower IFG-striatum connection strengths in the IA subjects represent slower suppressing of the responses through the indirect pathway, leading to failures in inhibiting responses.

Methods

Subjects. Twenty-eight adolescents with IA – as diagnosed by the modified Young's Diagnostic Questionnaire (YDQ) for Internet Addiction⁵² – and 27 well-matched healthy subjects participated in this study. The IA subjects were outpatients of the Second Xiangya Hospital of Central South University while the controls were recruited from high schools in Changsha. All subjects (and one of their parents) received a structured clinical interview from two experienced psychiatrists, which was based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). None of the participants in this study fulfilled any DSM-IV axis I disorders. Four healthy adolescents and 8 IA subjects were excluded from this study due to a failure to record behavioral data during the Go-Stop task. In addition, two IA subjects were removed from further analyses due to excessive head motion. Finally, 23 controls and 18 IA subjects were included in the analysis. There were no significant differences between the two groups in age (mean \pm S.D., IA: 15.1 \pm 1.4 years versus control: 15.2 \pm 0.5 years), ethnicity or education (Table 2, $p < 0.05$, two-sample *t* test).

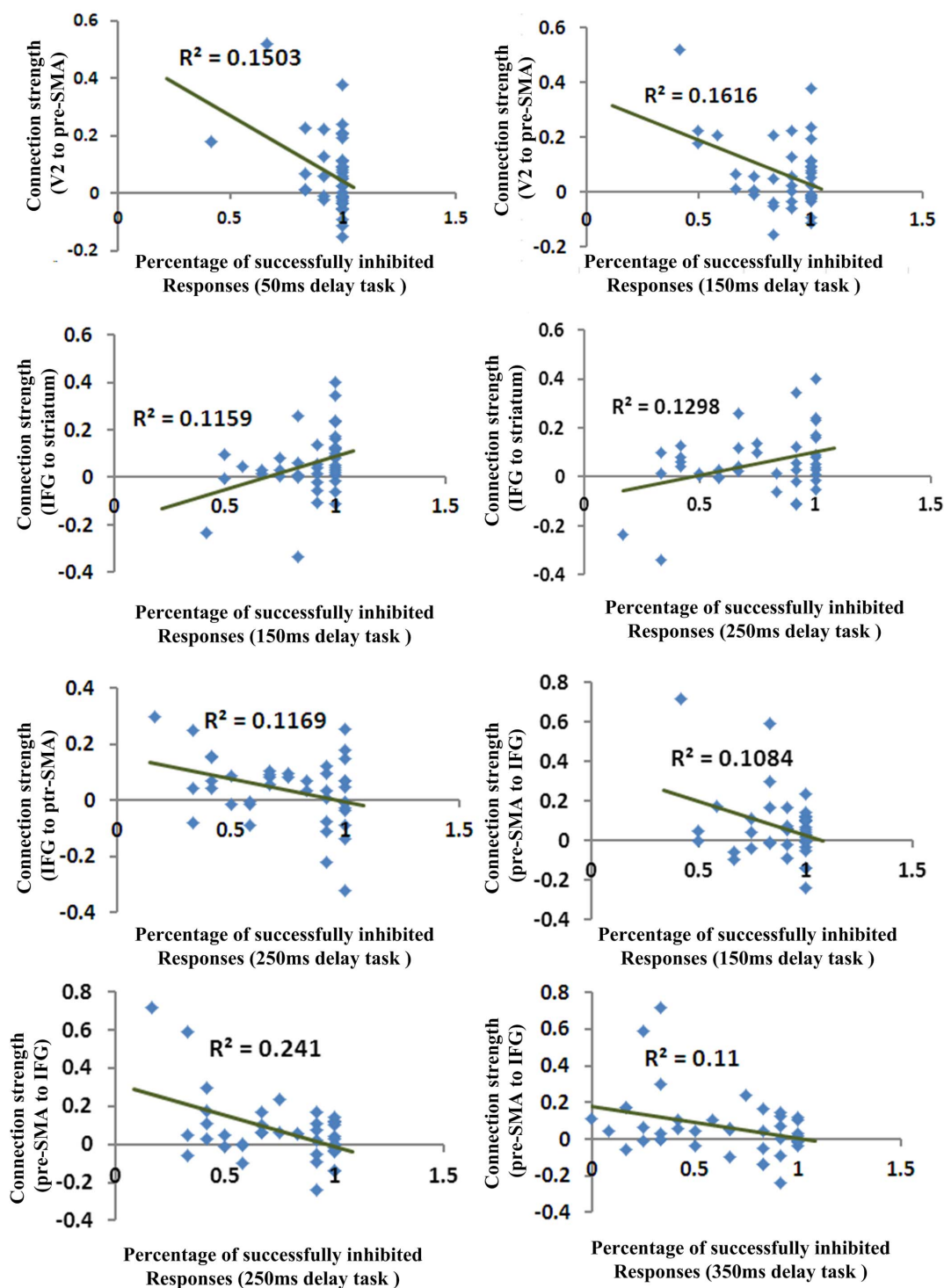


Figure 4 | Correlations between behavioral performance and connection strength.

Variable	Controls (n=23)	IA subjects (n=18)
	Mean(S.D.)	Mean(S.D.)
Age	15.2 (0.5)	15.1 (1.4)
Ethnicity	Han (Chinese)	Han (Chinese)
Education (years)	9.50(0)	9.28 (0.73)

All subjects' caretakers gave written informed consents. The study was conducted according to the principles in the Declaration of Helsinki and approved by the Ethics Committee of Second Xiangya Hospital of Central South University, Changsha, China.

YDQ is a questionnaire proposed by Young to diagnose Internet addiction based on the DSM-IV criteria for pathological gambling⁴. YDQ consists of eight criteria (supplemental Table 1). Young asserted that those who fulfill five or more of the eight criteria should be considered Internet-dependent. The initial Young's YDQ criteria were later modified by Beard and Wolf². They recommended that only those who met all of the first five criteria and at least one of the last three criteria should be considered Internet-dependent. The modified YDQ was used in the present study for the diagnosis of IA.

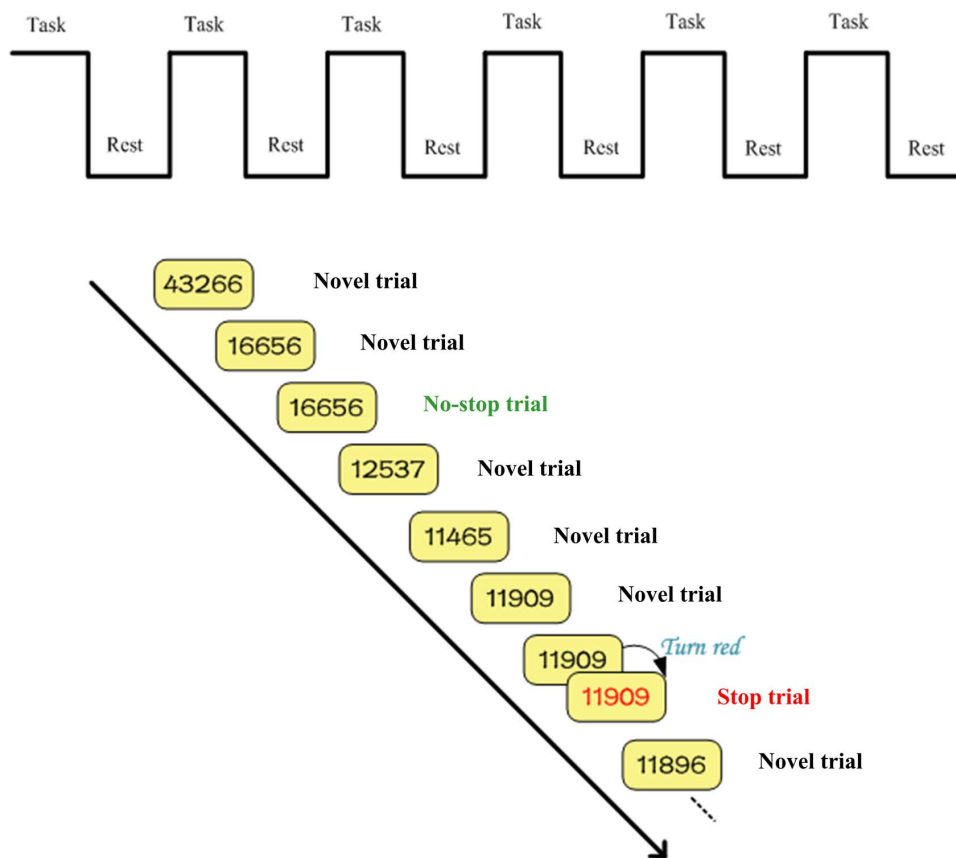


Figure 5 | Task structure for the Go-Stop paradigm.

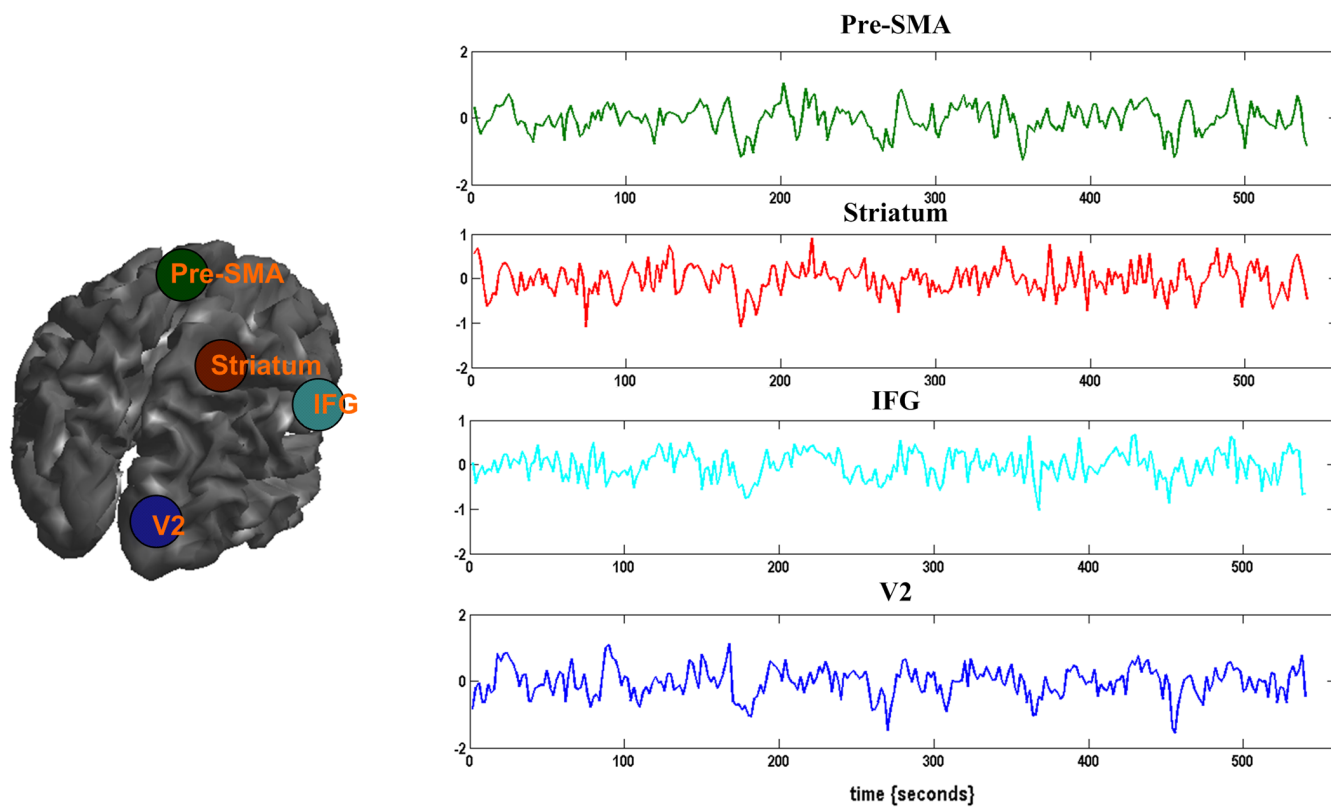


Figure 6 | The locations and time series of the ROIs; IFG, inferior frontal gyrus; pre-SMA, pre-supplementary motor area.



The Go-Stop Task. As shown in Fig. 5 this study used a block design. The scanning session began with a 70 s period of the Go-Stop task, which was followed by rest block that lasted for 20 s. The word ‘rest’ was fixated during the rest block, which was then followed by another task block. Rest and task blocks were repeated six times in each experiment and the scanning session lasted 9 min.

Go-Stop is a paradigm developed to assess the capacity to inhibit a response that has already been initiated. It requires participants to respond to a series of five-digit numbers presented in black on a white background. There are three trial types: no-stop, stop and novel trials (Fig. 5). Participants are told to respond with a button press to a number that is identical to the previous number presented in black, and this is a no-stop trial. A stop trial presents a number that matches the one before it, but it changes unpredictably from black to red at some specified stimulus onset asynchrony (50, 150, 250, or 350 ms) after stimulus onset. No button is pressed during a stop trial. Novel trials present randomly generated non-matching numbers in black. In the current study, the intervals (50, 150, 250, or 350 ms) – during which the target remained black (no-stop) before turning red (stop) – occurred with equal probability. Number stimuli were presented on the screen for 500 ms once every 2 s. The participants were instructed to respond to a no-stop trial before the number disappeared from the screen but withhold response to a stop trial or novel trial^{53,54}.

Image acquisition. A PHILIPS 3.0T whole-body scanner was used for acquiring the functional MRI images. A T2*-weighted gradient-echo EPI sequence (TR/TE = 2000/30 ms, 4 mm slice thickness, typically 36 axial slices, 64 × 64 matrix size, 24 × 24 cm FOV, 90°-flip angle) was used to measure blood oxygen level-dependent (BOLD) responses.

Data preprocessing. Preprocessing of the fMRI data used SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>). First, a six-parameter rigid body transformation (three rotations, and three translations) was used to realign the functional images to the first image of each session. Then images were normalized to a MNI EPI template with affine registration followed by a nonlinear transformation, using a voxel size of 2 × 2 × 2 mm. Finally, an 8-mm FWHM Gaussian kernel was used to smooth the data.

Statistical parametric mapping. Subject-specific responses were modeled using a general linear model (GLM) and standard (statistical parametric mapping) procedures: No-stop, stop and novel trials were modeled after convolution with a canonical hemodynamic basis function. The six motion parameters were included to model the movement correlated effects. In the first-level (within subject) analyses, we determined the contrast “stop>baseline”, which allowed us to identify brain regions that were activated or deactivated when the subject tried to inhibit responses. The resulting contrast images were then entered into the second-level (between-subject) analyses. Statistical parametric maps based on one-sample *t*-tests were used to illustrate brain activation during response inhibition for each group, while two-sample *t*-tests were performed to determine group differences of brain activation in the Go-Stop task. As this study focused on the response inhibition network, small volume correction was employed to a priori regions of interest: the IFG, striatum and pre-SMA. Sphere ROIs (radius = 25 mm) centered at peak coordinates as reported by Aron et al.³³ were constructed.

Dynamic causal modeling. Effective connectivity analysis was performed using DCM12. The basic idea behind DCM is to treat the brain as a dynamic input-state-output system that is driven by experimental inputs and produces outputs (BOLD responses). Each region has a (hidden) neuronal state corresponding to neuronal or synaptic activity and four (hidden) hemodynamic states representing a vasodilatory signal, blood flow, blood volume and deoxyhemoglobin content. At the neuronal level, the neuronal state equations describe how neuronal activity in one region is affected by neuronal activity in others and how these influences are modulated by experimental inputs. The neuronal state equations are supplemented with the hemodynamic state equations that transform the neuronal activity in each region to observed BOLD response⁵¹.

In this study, we used stochastic DCM. Stochastic DCM differs from conventional deterministic DCM by allowing for endogenous or random fluctuations in unobserved (hidden) neuronal and physiological states, known technically as system or state-noise^{54–57}. Compared to deterministic DCM, stochastic DCM has been shown to provide more accurate parameter estimates⁵⁴. Moreover, stochastic DCM can be used to study effective connectivity between brain regions in the resting state by exploiting spontaneous fluctuations in activity to estimate effective connectivity⁵⁸.

In order to reduce the model complexity, we concatenated the three inputs (the no-stop, stop and novel trials) to one input for the DCM analysis. In this case, we performed a GLM analysis with regressor for the task condition and six regressors represented the movement effects. For each subject, we determined the contrast “task>rest”.

Based on the group analysis – and on previous studies of the neural network associated with response inhibition – three ROIs were defined: the right IFG, the right striatum, and the left pre-SMA. Because subjects responded to visual stimuli (i.e., a series of five-digit numbers in black on a white background), activity within the motor system can be assumed to be driven by the visual system. Thus, we added a fourth region or node (V2) to our model. Because we did not detect significant activation of the STN during response inhibition in the subjects, this region was not included in the DCM. Subject-specific ROIs were centered on the local maximum of SPMs testing for “task minus rest”. For some subjects, the locations of the ROIs were slightly adjusted to make sure the same ROI for each subject was located within the same anatomical

gyrus as the group maximum. For the pre-SMA in one IA subject and the V2 in one healthy subject, the coordinates of the group maximum were used because we did not detect significant activation of the region in these subjects. The time series for all ROIs were extracted from a sphere region (radius = 6 mm). Fig. 6 shows the locations and the time series of the four ROIs.

For the DCM analysis, a fully connected model was first constructed. Specifically, visual input was modeled as a driving or exogenous input to V2 and subject-specific DCMs were fully and reciprocally connected (resulting in 12 connections among four nodes). Given our primary interest was to detect differences in effective connectivity between the groups; we did not model any bilinear or modulatory effects. In other words, we estimated the average connectivity under the task-set of response inhibition, assuming that endogenous fluctuations in neuronal activity (state noise) would model condition specific responses. The full connected model for each subject was inverted using generalized filtering as described previously⁵⁹. A network discovery scheme was then used to identify the optimal model pooling over all subjects⁶⁰. Subject specific parameter estimates (posterior means) under the optimal model were then taken to the second, between-subject level analysis using a classical random-effects analysis. This allowed us to summarize the findings from the subject-specific DCMs at the group level, using classical statistics (*t*-tests).

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Author contributions

F.L.C., L.Y.S., D.W.H. and S.Q.Y. designed the project. S.Q.Y. and D.W.H. performed the experiment and collected the data. B.J.L., J.L., Y.L. and G.P.Z. analyzed the data. B.J.L., K.J.F. and H.B.L. prepared the figures and wrote the manuscript.

Additional information

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