

## Morphometric Correlation of Impulsivity in Medial Prefrontal Cortex

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### Abstract

Impulsivity is a complex behaviour composed of different domains encompassing behavioural disinhibition, risky decision-making and delay discounting abnormalities. To investigate regional brain correlates between levels of individual impulsivity and grey matter volume, we performed voxel-based morphometric correlation analysis in 34 young, healthy subjects using impulsivity scores measured with Barratt Impulsivity Scale-11 and computerized Kirby's delay discounting task. The VBM analysis showed that impulsivity appears to be reliant on a network of cortical (medial prefrontal cortex and dorsolateral prefrontal cortex) and subcortical (ventral striatum) structures emphasizing the importance of brain networks associated with reward related decision-making in daily life as morphological biomarkers for impulsivity in a normal healthy population. While our results in healthy volunteers may not directly extend to pathological conditions, they provide an insight into the mechanisms of impulsive behaviour in patients with abnormalities in prefrontal/frontal-striatal connections, such as in drug abuse, pathological gambling, ADHD and Parkinson's disease.

### Keywords

Decision making; Impulsivity; Medial prefrontal cortex; Ventral striatum; Magnetic resonance imaging; Voxel based morphometry

### Introduction

Impulsive actions represents one of the major features of psychiatric conditions and chemical and behavioral addiction disorders (Alessi and Petry 2003; Barkley et al. 2001; Kirby et al. 1999; Kaladjian et al. 2011). Impulsivity is a complex behaviour composed of different domains encompassing behavioural dis-inhibition, risky decision-making and delay

discounting abnormalities (Dom et al. 2006; Reynolds et al. 2006; Swann et al. 2002). Brain areas like the dorsolateral prefrontal cortex (DLPFC), the medial prefrontal cortex (MePFC) including the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC) and the ventral striatum (VST) have all been reported to be critically involved in impulsive behaviours (Stuss et al. 1992; Rolls 2004; Bechara and Van Der Linden 2005). Patients with damage to those prefrontal regions show increased impulsivity on inhibition tasks (Bechara et al. 1999) and exhibit greater impulsivity and aggressive behavior compared to patients with other frontal cortex lesions (Grafman et al. 1996). Various neuropsychological frameworks have been used to explore the individual behavioral differences of impulsivity. Roughly there are two different approaches to evaluate impulsivity level: subjective self-reported measures of personality that rely on an individual's self-perception of behaviour and objective behavioural tasks that estimate the performance level (Dom et al., 2006). Both laboratory and self-report personality measures of impulsivity appear to be related to risk of psychopathology (Swann et al. 2002). How these two approaches can be combined to identify a common or overlapping neural network characterizing level of impulsivity is poorly investigated.

A few studies have investigated the relationship between structural changes in grey matter (GM) and impulsivity/self-control impairments (Koprivová et al. 2009; McAlonan et al. 2007). Previous observations using self-reported measurement reported an inverse correlation between impulsive behaviour and GM volume in the lateral OFC (Lui et al. 2009; Matsuo et al. 2009). Boes et al. (2009) showed that GM volume in the right MePFC predicted impulse control in adolescents. Studies using behavioural tasks such as the delay discounting paradigm have also demonstrated a relationship between impulsivity level and regional GM volume (Bjork et al. 2009; Schwartz et al. 2010) as well as white matter volume (Yu 2012). All together these reports demonstrated that structural changes at the cortical and subcortical level may be responsible for different degrees of impulsive behavior.

In this study, we investigated the relationship between individual impulsivity level measured, combining a self-reported method [i.e. Barratt Impulsivity Scale (BIS)] and objective behavioural test [i.e. computerized Kirby's delay discounting task (DDT)], and GM volume using a voxel-based morphometry (VBM) method. This method allows an unbiased assessment of regional variations in brain structures using structural magnetic resonance images (MRI), and when combined with regression analysis permits us to identify potential relationships between behaviour and local brain morphology as well as to determine interregional connectivity among remote brain areas (Worsley et al. 2005; Lerch et al. 2006). Our hypothesis was that impulsivity level would be correlated with the brain GM volume in those regions, i.e. the DLPFC, MePFC (including ACC and OFC) and VST, known to be associated with decision making processes and possibly reflecting a potential predisposing factor to impulsivity-related variations.

## Materials and Methods

### Subjects

Thirty four right-handed young healthy subjects (23.4 age  $\pm$  4.3 years; age range: 18–35 years; 11 females) were enrolled in this study. All participants were recruited through a local

advertisement. Prescreening was conducted by telephone before the subjects underwent a semi-structured interview during the first visit. Exclusion criteria included history of psychiatric and/or neurological disorders including epilepsy, any previous exposure to stimulant drugs, head injury, and migraine. To confirm handedness and emotional status, the Edinburgh Handedness Inventory and Beck Depression Inventory (BDI) were administered. Applicants who showed a laterality index less than 40 (left-handedness) for Edinburgh Handedness Inventory and depression score higher than ten were excluded. Brain MRI was performed within 1 week after the behavioural task performance for each subject. Written informed consent was obtained in all cases before study enrolment and the study protocol was approved by the Ethical Committee of the Centre for Addiction and Mental Health Research, University of Toronto.

### Behavioural Measurement

**Barratt Impulsivity Scale**—A self-report trait measure of impulsivity was collected using the Barratt Impulsivity Scale-11 (BIS). The BIS is a self-report questionnaire containing 30 questions, on a 4-point Likert scale reflecting frequency of occurrence. Scoring yields a total and three subscale scores: attentional (rapid shifts and impatience with complexity), motor (impetuous action) and non-planning (lack of future orientation) impulsiveness (Patton et al. 1995). Higher scores demonstrate higher impulsivity.

**Kirby's Delay Discounting Task**—As a laboratory measure of impulsivity, computerized Kirby's delay discounting task (DDT) was used (Kirby et al. 1999). The task was composed of 27 trials; in each trial the amounts of monetary reward for immediate and delay options were decided by the fixed  $k$  value and the delay time was based on the hyperbolic function of delay discount,  $V = A/(1 + kD)$ , where  $V$  is the value of the delayed outcome,  $A$  is the delayed reward,  $D$  is the length of the delay, and  $k$  expresses the steepness of the discount function (de Wit et al. 2002; Mitchell 1999; Richards et al. 1999). Based on this function, higher  $k$ -values are associated with a preference for immediate but small rewards and lower  $k$ -values indicate a preference for delayed but large rewards. Thus, low  $k$ -values are an index of minor impulsivity. Subjects were instructed that they had to make preference judgments about hypothetical rewards shown on a computer screen. All reward choices were made by pressing either the ← or → key with the subject's dominant hand (right hand for all subjects). Choice options were presented on the screen until response selection; the inter-stimulation interval was 2 s. The trial order was fixed across the subjects based on Kirby's inventory (Kirby et al. 1999).

The individual discounting values ( $k$ ) were obtained from all subjects. The detailed method for computing individual discounting values ( $k$ ) has been described elsewhere (Kirby et al. 1999; Kirby and Petry 2004). The  $k$ -values were estimated as the geometric mean between the lowest implied indifference  $k$ -value in which subjects chose the delayed option, and the highest implied indifference  $k$ -value in which subjects chose the immediate option. For all analyses the distributions of  $k$ -values were approximately normalized using the natural-log transformation [ $\ln(k)$ ].

## Structural MRI

MRI scans were obtained using a 1.5T high-resolution MRI scanner (GE Signa EXCITE). T1-weighted 3D gradient echo imaging (FSPGR with repetition time = 11.9 ms, echo time = 5 ms, flip angle = 40°, field of view = 24 cm, slice thickness = 1 mm, NEX = 1, matrix size = 256 × 192) was performed to obtain 176 images covering the entire brain.

## Voxel-Based Morphometry (VBM) Analysis

Images were processed using a VBM protocol implemented in VBM8 tool-box (<http://dbm.neuro.uni-jena.de/vbm/>) of the SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>) with default parameter incorporating the DARTEL toolbox. Images were bias-corrected, tissue classified, and registered using linear (12-parameter affine) and non-linear transformations, within a unified model (Ashburner and Friston 2005). Final modified GM images were smoothed with an isotropic Gaussian kernel of 8 mm full-width at half maximum. To exclude from the statistical analysis pixels assigned by the segmentation to GM with low probability values and pixels with a low inter-subject anatomical overlay after normalization, the mean image of normalized GM from all subjects was used to create a GM mask, whose threshold was set at a value of 0.30 (pixels with computed GM fraction values >30 % were selected) and then used as an explicit mask for the statistical analysis.

In SPM8 voxel-wise multiple regression analysis of GM images and impulsivity scores with age and total brain volume as nuisance variables was performed with a  $P$ -threshold <0.001 uncorrected and an extent threshold of 100 continuous voxels. Small volume correction (SVC) for regional multiple comparisons was performed on regions of interest (ROI) associated with impulsivity level (i.e. DLPFC, MePFC and VST) by using a sphere with 10 mm-radius centered in the peak coordinates. SVC results are reported as significant at  $P < 0.05$  with family-wise error correction on the voxel-level. Bonferroni correction was applied for multiple tests of correlation for BIS subscales.

All the analyses involving behavioural data were performed with SPSS software (SPSS Inc., Chicago), and the significance level was set at  $P < 0.05$ . For the visualization of the  $t$ -score statistics (SPM{ $t$ } map), the significant voxels were projected onto the ICBM152 brain mask image thus allowing anatomic identification using BrainNet viewer (<http://www.nitrc.org/projects/bnv/>) with a  $P$ -threshold <0.001, uncorrected. The MNI coordinate of the local maximum of each cluster was converted into Talairach coordinates (Talairach and Tournoux 1988) and listed in Tables 2 and 3 along with  $T$ -value and cluster size.

## Results

The mean ( $\pm$ SD) and range for BIS and log transformed  $k$ -value [ $\ln(k)$ ] are shown in Table 1. The mean BIS total score for all subjects was 58.7 (SD = 10.0, range 36–78), which is representative of the normal range for the general population (Spinella 2007). The mean  $\ln(k)$  of DDT was  $-6.5$  (SD: 2.5, range was  $-12.3$  to  $-2.2$ ). BIS total score did not correlate with  $\ln(k)$  (Pearson's correlation coefficient  $r = 0.28$ ,  $P = 0.11$ ). Within the sub-scores, the non-planning impulsivity scale of BIS showed significant positive correlation with  $\ln(k)$  (Pearson's correlation coefficient  $r = 0.35$ ,  $P < 0.05$ ) (Fig. 1) and a negative correlation with

age (Pearson's correlation coefficient  $r = -0.044$ ,  $P < 0.05$ ), suggesting that lack of careful thinking and planning was associated with higher delay discounting tendency and younger age. No significant sex dependent difference was found for either the total or subscales of BIS or  $\ln(k)$ .

The BIS total score showed a correlation in the ROIs defined in our a priori hypothesis, i.e. MePFC, including the ACC (BA 24/32) and medial OFC (BA10), and DLPFC (BA 46) (Table 2; Fig. 2). Additionally, in the whole brain VBM analysis, positive correlations with level of GM volume were found in middle/inferior temporal ( $x = -50$ ,  $y = 0$ ,  $z = -29$ ,  $T = 4.01$ , BA 20/21) and parahippocampal gyri ( $x = 35$ ,  $y = -41$ ,  $z = -3$ ,  $T = 4.64$ , BA 19/35), implying that individuals who showed higher GM volume had higher impulsive tendency.

When correlation analysis was performed for each score of the BIS sub-scales, the GM volume in ROIs correlated with the non-planning impulsivity scale of BIS at the level of the left pre/subgenual ACC (BA 32) and DLPFC (BA 47), bilateral middle ACC (BA 24/32), and right medial OFC (BA 11). In addition, a positive correlation was observed in the superior temporal gyrus ( $x = -48$ ,  $y = 14$ ,  $z = -6$ ,  $T = 5.95$ , BA 38) and the right parahippocampal gyrus ( $x = 38$ ,  $y = -48$ ,  $z = 1$ ,  $T = 6.76$ , BA 19) in whole brain level analysis. The left DLPFC (BA 10/46) and bilateral MePFC GM (BA 10/11) volumes were significantly correlated with the attention related impulsivity scale (Table 2; Fig. 2). There were no significant correlations between regional GM volumes and the motor impulsivity scale of BIS.

The  $\ln(k)$  of the DDT showed some commonalities with the BIS, i.e. positive volumetric correlation in the MePFC including the ACC (BA 24/32) and medial OFC (BA 11) (Table 3; Fig. 3). In addition, GM volume showed a significant negative correlation at the level of the bilateral ventral putamen implying that individuals with lower GM volume in VST had higher impulsive tendency (Table 3; Fig. 3).

## Discussion

Using VBM analysis, we observed a relationship between levels of impulsivity and GM volume in several brain structures associated with decision making and the reward network (i.e. DLPFC, MePFC and VST). In particular, while the non-planning impulsivity score presented a widespread correlation within the MePFC including the dorsal ACC and medial OFC, the correlation of attention related impulsivity subscore was more limited to the medial OFC area. Whereas the origin of these differences can be debatable, we could speculate that the larger correlation area observed in the non-planning impulsivity score may be related to the specific and stronger contribution of these regions in the MePFC in reward-based decision-making and learning (Bush et al. 2002) associated with this task.

Our observation seems to complement previous reports (Matsuo et al. 2009) where instead at the level of the lateral part of the OFC a negative correlation was observed between GM and BIS measured impulsivity. This is not surprising given that it is well known that the medial and lateral OFC have distinct neuro-anatomical connections (Ferry et al. 2000; Kondo et al. 2003, 2005) and functional roles (Noonan et al. 2010; Mar et al. 2011; Bechara 2005).

Experimental studies in animals seem to support this different function with a dissociation between the effects of medial and lateral OFC lesions in value guided decision making in macaque monkeys (Noonan et al. 2010). Thus, it seems reasonable to think that the positive relationship between GM volume and impulsivity in the MePFC/medial OFC may be the result of the engagement of reflective system (Bechara 2005) during decision making in subjects with higher impulsivity. Previous studies showed GM volume correlation in the OFC with motor impulsivity (Matsuo et al. 2009). The lack of a similar correlation in our study may be due to the functional differences described above between the lateral and medial OFC and the fact that the latter region may be less sensitive to motor-related impulsivity.

The DLPFC as well was associated with a positive relationship between GM volume and impulsivity level measured with BIS. This correlation seems particularly strong in relation to non-planning and attention/cognitive impulsivity sub-scores but not with motor impulsivity. So far, certain anatomical studies seemed to endorse this association between DLPFC and impulsivity level (Bjork et al. 2009), while others do not (Boes et al. 2009; Matsuo et al. 2009). In support of the former, there are also fMRI (Monterosso et al. 2007; McClure et al. 2004) and neurophysiological experiments conducted either with repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (Fecteau et al. 2007; Koch et al. 2005; van't Wout et al. 2005). By applying rTMS to the right DLPFC in young healthy subjects, we were able to temporarily affect impulsivity level as measured by the DDT (Cho et al. 2010). In particular, rTMS of the right DLPFC induced healthy subjects to trade immediate rewards for delayed larger rewards. We proposed that these results were due to a removal of inhibitory control exerted by this prefrontal area (Aron et al. 2004; Conway and Fthenaki 2003) or by altering time perception (Koch et al. 2003).

Functional interactions between the DLPFC and MePFC have been documented both during behavioral tasks (MacDonald et al. 2000; Cole and Schneider 2007) and brain stimulation (Ohnishi et al. 2004; Knoch et al. 2006; Cho and Strafella 2009; Mayberg et al. 2005). It is thought that these prefrontal areas are part of multiple nodes in a large network of cortical and subcortical areas involved in choice of reward that varies over time (Hariri et al. 2006; Kable and Glimcher 2007; McClure et al. 2004; Xu et al. 2009). A recent study also showed the importance of context-dependent communication between the DLPFC and MePFC during normative decision making that related to monetary reward (Baumgartner et al. 2011).

The impulsivity level measured by DDT showed some commonalities with the BIS in the correlation analysis with GM in several brain areas such as the ACC and medial OFC. The ACC is known to be engaged in socio-cognitive processing, such as the selection of consequential versus inconsequential choices (Turk et al. 2004). Interestingly, because most BIS items are focused on the behavioural pattern in a social context and the DD paradigm also mimics economic decision making in real life, the positive correlation of BIS and DD levels [ $\ln(k)$ ] with ACC GM volume may indicate that the social context inherent in the task and questionnaire items may contribute to decision making. Other neuroimaging studies showed a similar correlation in the ACC. For example, in healthy subjects, activation in the ACC was positively correlated with impulsivity level during a task requiring response

inhibition suggesting a significant regulatory role for this region (Brown et al. 2006). The pregenual ACC covaried with the subgenual part of the ACC (BA 25), a target area of the mesocortical dopamine system originating in the ventral tegmental area (Williams and Goldman-Rakic 1998) and also connected with the amygdala (Freedman et al. 2000). Even if it is unclear at the moment if these changes in GM volume, observed in ours and related studies, are part of a compensatory mechanism or primary phenomenon, our observations seem to suggest that the ACC provides significant regulatory input in modulating the level of impulsivity.

Reduced GM volume in the bilateral ventral putamen was associated with higher impulsivity levels measured by DDT in this study. This observation may not be surprising given that, contrary to DDT, BIS measures impulsive personality traits rather than sensitivity to reward (Moeller et al. 2001). This subcortical area is critical for processing reward: activation of this area occurs in response to rewarding stimuli (O'Doherty 2004) regardless of gender, age or race, and valence (positive vs. negative) (Hariri et al. 2006). Striatal dopamine is also implicated in impulsive decision-making behaviours (de Wit et al. 2002). Recent fMRI studies showed that the VST may encode the amount of potential financial gain (Kable and Glimcher 2007) and reward delays in a DDT (Xu et al. 2009). Specifically, the ventral putamen has been suggested to be implicated in encoding the valence of events regardless of the outcome (Mattfeld et al. 2011).

Related to impulsive control, Bechara (2005) provided an interesting conceptual framework with two separate but interacting neural systems that control decision making, i.e. a hyperactive impulsive system (i.e. amygdala-VST) and a deficient reflective/executive system (i.e. PFC), both responsible for impulsive choice and behavior. However, how the balance of these two systems is controlled in the normal functioning healthy brain is still not clear. In our study, we identified a morphological correlation with impulsivity score at the level of the parahippocampal gyrus. This region is functionally and anatomically interconnected with the MePFC (Carmichael and Price 1996) and generally associated with emotional regulation, experience of loss or punishment and spatial memory (Gilbert et al. 2010; Elliott et al. 2000; Ploner et al. 2000; Moscovitch et al. 2005). Thus, in our case, it may be possible that the parahippocampal gyrus may contribute to the emotional salience associated with the decision making process. This is also consistent with previous studies demonstrating the involvement of this region in impulsive behaviour (Völlm et al. 2007; Soloff et al. 2008; Carmona et al. 2005; Cilia et al. 2008).

In summary, our voxel-based VBM analysis showed that impulsivity appears to be reliant on a network of cortical and subcortical structures, emphasizing the importance of brain networks associated with reward related decision making in daily life as morphological biomarkers for impulsivity in a normal healthy population. While our results in healthy volunteers may not directly extend to other pathological impulsive conditions, they provide an insight into the etiology of development of impulsive behaviour in groups of patients with abnormalities in fronto-frontal/fronto-striatal connections (Cilia et al. 2011; Konrad and Eickhoff 2010), such as in drug abuse, pathological gambling, ADHD and Parkinson's disease.

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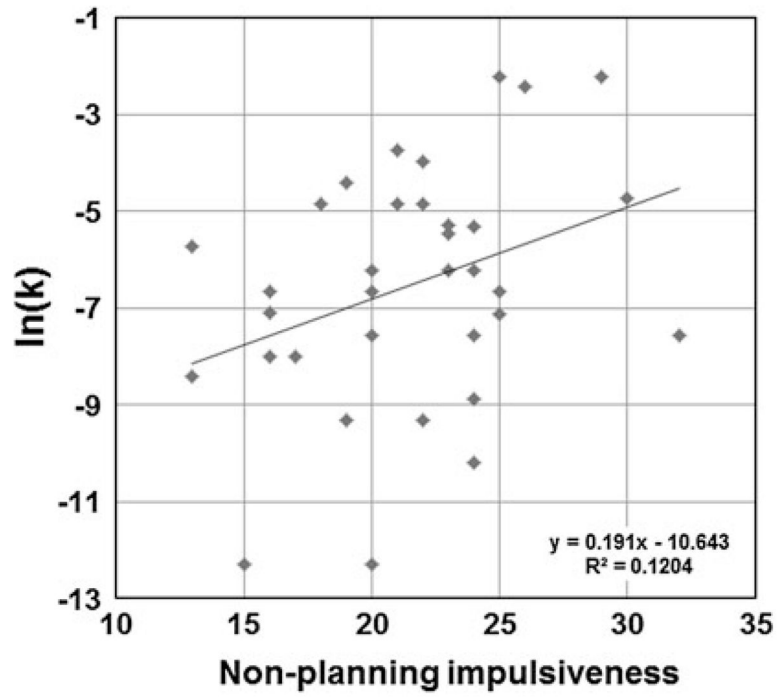


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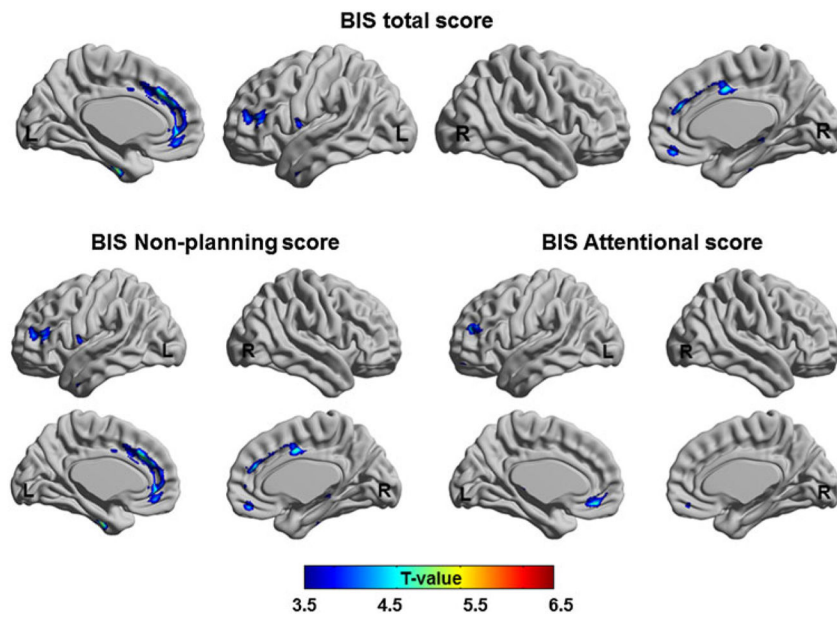
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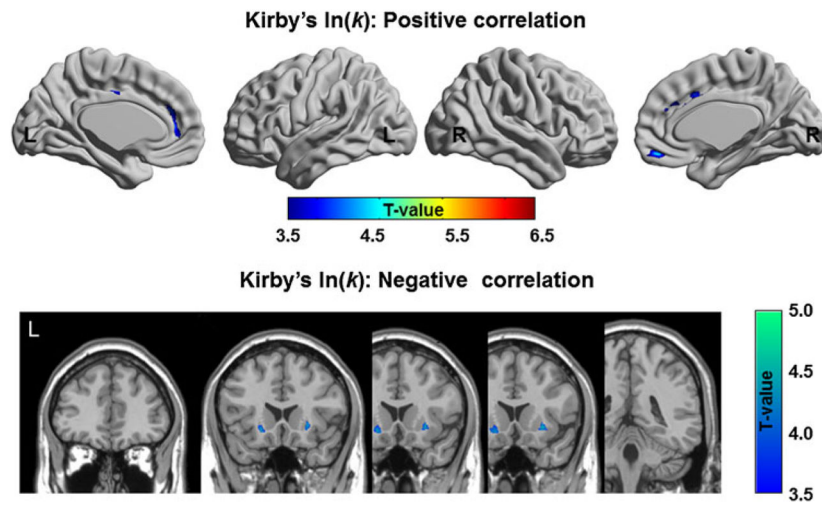
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**Fig. 1.** Positive correlation between Barratt impulsivity scale (BIS) non-planning impulsivity score and delay discounting task (DDT)  $\ln(k)$  (Pearson's correlation coefficient  $r = 0.35$ ,  $P < 0.05$ )



**Fig. 2.** Brain regions show the positive correlation of GM volume with BIS total score (*upper figure*) and BIS sub-scores (*lower figure*)



**Fig. 3.** Brain regions show the positive and negative correlation of GM volume with  $\ln(k)$

**Table 1**

Results of impulsivity level using self-reported (BIS) and behavioural task (Kirby's DDT)

	Mean ( $\pm$ SD)	Range
BIS total	58.7 (10.7)	36–78
Non-planning	21.5 (4.5)	13–32
Attention	15.3 (3.6)	14–21
Motor	21.9 (4.5)	14–31
Kirby's $\ln(k)$ *	-6.5 (2.5)	-12.3 to -2.2

\* Log transformed  $k$ -value

**Table 2**

Regions showing the GM volumetric correlation with BIS total and sub-scales

Region	BA	Coordinates <sup>d</sup>			T-score	SVC	Corrected P value	Cluster Size <sup>b</sup>
		X	Y	Z				
<i>Positive correlation with BIS total score</i>								
Lt anterior cingulate gyrus	BA 24	-9	37	-2	5.29	0.001	3820	
	BA 32	-6	32	23	5.17	0.001		
Lt medial frontal gyrus	BA 10	-3	43	-7	5.22	0.001		
Lt middle frontal gyrus (DLPFC)	BA 46	-41	43	9	4.30	0.007	635	
<i>Positive correlation with non-planning impulsivity score</i>								
Lt anterior cingulate gyrus	BA 32	-2	46	-2	5.87	0.0001	3561	
Rt middle cingulate gyrus	BA 24	5	-2	36	5.60	0.0001		
Lt middle cingulate gyrus	BA 32	-3	15	35	5.17	0.0001		
Lt middle frontal gyrus (DLPFC)	BA 47	-41	31	2	4.75	0.003	306	
Rt orbitofrontal gyrus	BA 11	5	22	-20	4.37	0.008	131	
<i>Positive correlation with attentional impulsivity score</i>								
Lt medial frontal gyrus	BA 10/11	-3	37	-14	5.06	0.001	672	
Rt medial frontal gyrus	BA 11	8	45	-17	4.03	0.01		
Lt middle frontal gyrus (DLPFC)	BA 10/46	-41	47	15	4.90	0.002	611	

L left, R right, *DLPFC* dorsolateral prefrontal cortex, *BA* Brodmann's area

<sup>a</sup>Talairach coordinate (mm), *SVC* small volume correction (radius = 10 mm from statistical peak) was applied using a reporting criterion of  $P < 0.05$  with family wise error corrected for multiple comparison

<sup>b</sup>No. of voxels



**Table 3**

Regions showing the correlation between GM volume and  $\ln(k)$

Region	BA	Coordinates <sup>d</sup>			T-score	SVC	Corrected P value	Cluster size <sup>b</sup>
		X	Y	Z				
<i>Positive correlation</i>								
Rt medial frontal gyrus	BA 11	11	46	-17	5.32	0.001	238	
Rt orbitofrontal gyrus	BA 11	3	56	-20	3.81	0.005		
Lt medial frontal gyrus	BA 9	-12	38	18	5.07	0.001	609	
Lt anterior cingulate gyrus	BA 24	-8	31	2	4.51	0.004		
Rt anterior cingulate gyrus	BA 32	17	15	33	4.50	0.004	265	
Lt middle cingulate gyrus	BA 24	-3	-11	36	4.03	0.01	102	
<i>Negative correlation</i>								
Lt ventral putamen		-29	11	-8	4.48	0.005	226	
Rt ventral putamen		29	17	-5	4.33	0.006	120	

L left, R right, BA Brodmann's area

<sup>a</sup>Talairach coordinate (mm), SVC small volume correction (radius = 10 mm from statistical peak) was applied using a reporting criterion of  $P < 0.05$  with family wise error corrected for multiple comparison

<sup>b</sup>No. of voxels