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ORIGINAL PAPER

Shuji Asahi · Yasumasa Okamoto · Go Okada · Shigeto Yamawaki · Norio Yokota

Negative correlation between right prefrontal activity during response inhibition and impulsiveness: A fMRI study

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Abstract Behavioral disinhibition in Go/No-Go task is thought to be associated with impulsiveness in humans. Recent imaging studies showed that neural circuits involving diverse areas of the frontal cortex and other association cortex sites such as the parietal cortex are implicated in the inhibition of response during No-Go trials. The aim of the present study was to investigate the association between regional cerebral activation during No-Go trials and impulsiveness. Seventeen right-handed healthy volunteers participated in the study. We used functional magnetic resonance imaging to measure the brain activation during a Go/No-Go task. The Barratt Impulsiveness Scale, 11th version (BIS-11) was used to measure impulsiveness. Activated regions included the right middle frontal gyrus and the inferior parietal lobe, which is consistent with previous neuroimaging studies. A negative correlation was observed between the motor impulsiveness of BIS-11 and No-Go-related activation in the right dorsolateral prefrontal cortex (RDLPFC). Our results suggest that the RDLPFC is the area most sensitive to differences in individual motor impulsiveness and its activity may be an indicator of the individual capacity for response inhibition.

Key words response inhibition · fMRI · right dorsolateral prefrontal cortex (RDLPFC) · impulsiveness · BIS

Sh. Asahi · Y. Okamoto · G. Okada · Sh. Yamawaki, M.D., Ph.D. (✉)
Department of Psychiatry and Neurosciences
Graduate School of Biomedical Sciences
Hiroshima University
1-2-3 Kasumi, Minami-ku
Hiroshima, 734-8551, Japan
Tel.: +81-82/257-5205
Fax: +81-82/257-5209
E-Mail: yamawaki@hiroshima-u.ac.jp

N. Yokota
Hiroshima Prefectural College of Health and Welfare
Hiroshima, 723–0053, Japan

Introduction

Impulsiveness is a dimensional personality trait that is important for a wide range of different human behaviors. Although a strict definition of impulsiveness is difficult to establish, biological, psychological and social studies have regarded impulsiveness as 'a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others' [34]. Recent laboratory investigations of impulsiveness showed two dominant models: (1) *Reward-delay impulsivity*, which is the inability to delay reward and leads to an increased tendency to choose immediate small rewards over larger delayed ones [35]; and (2) *Rapid-response impulsivity*, which is the inability to conform responses to environmental context and leads to errors of commission on tests that require careful checking of stimuli [16]. The latter model appeared to be more closely related to trait impulsiveness, which was measured by the Barratt Impulsiveness Scale (BIS), a popular self-reporting impulsiveness scale [37], and was increased in subjects with a lifetime Axis I or Axis II diagnosis [49].

The ability to inhibit behavioral responses that are inappropriate in the current context is a response inhibition essential for normal behavior, and is thought to be associated with *Rapid-response impulsivity* in humans. This inhibitory function has been investigated frequently using the Go/No-Go task, in which the participants are required to refrain from responding to designated items within a series of stimuli. The prefrontal cortex (PFC) has been implicated in behavioral inhibition, based on animal, clinical and neuroimaging studies. Studies in monkeys demonstrated that lesions in the PFC resulted in difficulties in behavioral inhibition [8, 24, 45], as well as the studies of patients with lesions in the same region [22]. Recent neuroimaging studies using PET or fMRI have shown a right hemispheric dominance of inhibitory control that involves diverse areas of

the frontal cortex and other association cortex sites, such as the parietal cortex, which are implicated in response inhibition during No-Go trials [21, 26, 30]. Although human impulsiveness was revealed to associate with some biological markers [1, 17, 42, 50], the region of the brain that is directly correlated with human impulsiveness is still unclear.

Some experiments used only behavioral laboratory measurements of impulsiveness [11, 21], which do not incorporate the cognitive or social aspects of impulsiveness and do not measure long-term patterns of behavior. This may explain the inconsistency in the findings of those previous studies [9, 33, 38]. Another way to examine impulsiveness is to use self-reporting measurements such as BIS, which has the advantage of generating information on a variety of types of acts and on whether these acts continue as long-term patterns of behavior. In general, a closer association and a greater consistency has been demonstrated among different self-report impulsiveness scales [3, 9, 15].

The aim of the present study was to clarify the brain areas associated with impulsiveness, as measured by BIS-11. Based on the studies cited above, we hypothesized that the degree of activation in some areas within the right hemispheric dominance of neural networks was correlated with the degree of impulsiveness.

Methods

Subjects

Seventeen right-handed healthy volunteers (10 men and 7 women), aged 23–30 years (mean: 25.1 years), and with no history of neurological or psychiatric illness, participated in the study. Handedness was assessed by the Edinburgh Handedness Inventory [36]. The subjects were recruited from the Kansai area in Japan and were paid ¥7,000 for their participation in the study. The study was conducted under a protocol that was approved by the Ethics Committee of Hiroshima University School of Medicine. All subjects submitted informed written consent of their participation.

Barratt Impulsiveness Scale, 11th version

The BIS-11 [37], a short questionnaire designed to measure impulsiveness, has been validated in impulsive and normal populations. The questionnaire contains a total of 30 items, each of which is answered on a 4-point Likert scale (rarely/never = 1, occasionally = 2, often = 3, almost always/always = 4), and the level of impulsiveness is calculated by summing up the scores for each item. All items are defined as identifying impulsiveness within the structure of related personality traits and are divided into three subscales: attention (inattention and cognitive instability), motor (motor impulsiveness and lack of perseverance), and non-planning (lack of self-control and intolerance of cognitive complexity). The Japanese version of the BIS-11 was developed using a back-translation method and was judged to be a reliable and valid measure in the Japanese population [47]. Subjects completed the BIS-11 after the task procedure.

Experimental tasks

The task consisted of eight alternating 36-s epochs of Go and No-Go conditions. During the experiment, subjects viewed a series of letters once every 1500 ms and responded with a key press to every letter except the letter 'X', to which they were instructed to withhold response. All subjects responded using the forefinger of the right hand. Stimulus duration was 500 ms and the interstimulus interval was 1000 ms for both conditions. Subjects were instructed to try to respond while the stimulus was on the screen. In the Go (control) condition, subjects were presented a random sequence of letters other than the letter 'X'. In the No-Go condition, subjects were presented with the letter 'X' 50 % of the time, thus requiring a response to half the trials (Go trials) and a response inhibition to the other half (No-Go trials). The high frequency of targets was maintained across the entire experiment, which generated a compelling tendency to respond. In order to ensure correct performance, the subjects were trained outside the task scanner until they understood the task completely. Motor responses were made using a fiber-optic response pad (Current Designs Inc, Philadelphia). The task consisted of eight blocks, each of which continues without being preceded by an instruction. The subjects could not distinguish the boundary between the conditions; therefore, different strategies are not imposed on the subject for the different conditions.

fMRI acquisition

Functional magnetic resonance imaging (fMRI) was performed using a Magnex Eclipse 1.5T Power Drive 250 (Marconi Medical Systems, USA). A time-course series of 107 volumes was acquired with T2*-weighted, gradient echo, echo planar imaging (EPI) sequences. Each volume consisted of 38 slices, and the slice thickness was 4.0 mm with no gap to cover the entire cerebral and cerebella cortex. The interval between two successive acquisitions of the same image (TR) was 4000 ms, echo time (TE) was 55 ms, and the flip angle was 90°. The field of view was 256 mm, and the matrix size was 64×64, giving voxel dimensions of $4.0 \times 4.0 \times 4.0$ mm. After functional scanning, structural scans were acquired using Tl-weighted gradient echo pulse sequence (TR = 12 ms; TE = 4.5 ms; Flip angle = 20°; FOV = 256 mm; voxel dimensions of $1.0 \times 1.0 \times 1.0$ mm), which facilitated the localization and coregistration of functional data.

Analysis

The image data were analyzed by statistical parametric mapping (SPM99 software from the Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks Inc., Sherborn, MA). The first three volumes of each fMRI run (prescan period) were discarded because the magnetization was unsteady. The remaining 104 volumes were used for the statistical analysis. Images were corrected for motion and realigned, using the first scan of the session as a reference. T1 anatomical images were coregistered to the first functional scans and aligned to the T1 template included in SPM99. The calculated nonlinear transformation was applied to all functional images for spatial normalization. Finally, the functional images were smoothed with an 8 mm full-width, half-maximum (FWHM) Gaussian filter. Using group analysis according to a random effect model [18], we identified regions that showed significant responses to the No-Go condition compared with that of the Go condition as areas related to response inhibition. The group analysis consisted of two levels. In the first level, the signal time course of each subject was modeled with a delayed box-car function convolved with a hemodynamic response function in the context of a general linear model. One contrast image per subject was created by contrasting the No-Go conditions with the Go conditions. These images were entered into a one-sample t-test, which allowed us to identify regions of the brain that were significantly activated by the response inhibition function during the No-Go condition as compared to the Go condition. The resulting foci were then characterized in terms of spatial extent (k) and peak height (u). The significance of each region was estimated using distribution approximations from the theory of Gaussian fields. This characterization is in terms of the probability that a region of the observed number of voxels (or greater) could have occurred by chance (extent threshold) over the entire volume analyzed. After locating and analyzing areas of the brain that showed sig-

nificant activation during the No-Go condition, we then performed a regression analysis on these areas only, to determine the association between the magnitude of brain activation in each area and the scores of the BIS-11. Activations were reported if they exceeded $p < 0.001$ (uncorrected) on the single voxel level and $p < 0.05$ (corrected) on the cluster level. In regression analysis, we masked with the regions that showed significant responses to the No-Go condition compared with that of the Go condition, as the areas related to response inhibition described above, to avoid identifying regions that were not activated for the No-Go condition compared with the Go condition. However, when using a lower threshold, an activation that was at a lower level but consistent with the significant activation noted above was seen over more widespread areas of the brain. This occurred because the threshold for this mask was set at $p < 0.05$ and larger areas are included in the final analysis of the response inhibition data. Therefore, significance was considered at a threshold of $p < 0.001$ and an extent of > 40 contiguous voxels. Labels for brain activation foci were obtained in Talairach coordinates using the Talairach Demon software, which provides an accuracy similar to that of neuroanatomical experts [28].

Behavioral analysis

Errors of commission (response to 'X') and omission (not to response to targets) were recorded, and the average response times to targets were calculated for each subject.

Results

Behavioral and BIS-11 results

Subjects performed well on the task, making a few commission errors (7.3 %) and a few omission errors (1.3 %). The response times to targets averaged 325.8 ± 20.8 ms. Average scores of the total BIS-11, attention-key, motor-key and non-planning-key were 68.9 ± 11.0, 19.7 ± 3.3, 21.1 ± 4.1 and 28.1 ± 5.3, respectively. Some correlation was detected among the BIS-11 scales. The total score of BIS-11 was strongly correlated with all of the 3 subscales (attention-key: $r = 0.69$, $p < 0.01$; motor-key: $r = 0.89$, $p < 0.01$; non-planning-key: $r = 0.93$, $p < 0.01$). Among the subscales, the non-planning-key and attention-key ($r = 0.51$, $p < 0.05$), or non-planning-key and motor-key ($r = 0.79$, $p < 0.01$) were correlated. There was also a trend between attention-key and motor-key, though not significant ($r = 0.48$, $p = 0.05$). These results were natural because the BIS-11 has sufficient internal consistency reliability [47]. No correlation was observed between the performance data (i. e., number of commission errors or omission errors, average response time to targets) and the BIS-11 scores.

fMRI data

For fMRI data analysis, the threshold for activation was set at $p < 0.001$ for voxel level. In Fig. 1 and Table 1, the activation, which was corrected for multiple comparisons at the extent threshold of $p < 0.05$, is shown. Four independent areas of activation, which were predominantly right-lateralized, were observed to underlie response inhibition. These areas, including the Talairach coordinates of their centers-of-mass, are presented in Table 1. The No-Go condition, in comparison to the Go condition, resulted in the significant activation of the right middle and superior temporal gyrus, the right precentral gyrus, the right middle frontal gyrus, and the right cuneus and precuneus.

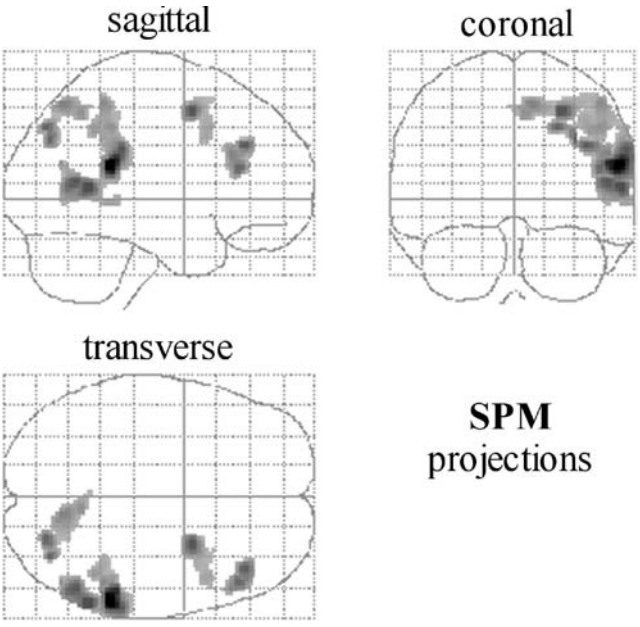

Fig. 1 Statistical parametric maps of brain regions (on the second level group analysis for the 17 subjects) showing significant activation associated with the NO-GO condition, compared with the GO condition at a statistical threshold of $P < 0.001$ (uncorrected) on the single voxel level and $P < 0.05$ (corrected) on the cluster level. For exact coordinates, see Table1. Clusters of activation are shown as through-projections onto representations of standard stereotactic space. *Sagittal* side view; *coronal* view from back; *transverse* view from above

Regression analysis revealed a significant negative correlation between the motor-key score of BIS-11 and the magnitude of brain activation during response inhibition in the right middle frontal gyrus (x, y, z = 34, 22, 29; area 9; t-value = 5.66; 42 voxels; $r = -0.93$; $p < 0.01$) showed in Fig. 2A, B. Other BIS-11 scores (i. e., total BIS-11, attention-key and non-planning-key) did not show a significant association with the magnitude of brain activation during response inhibition. Furthermore, no significant correlation was observed between the performance data (i. e., the number of commission errors and omission errors, response time) and the magnitude of brain activation during response inhibition.

By analyzing the mean percentage signal changes in the regions shown in Fig. 1 and Table 1, we sought to find the possible functional connectivity among the regions concerning response inhibition. Consequently, we detected a correlation between the areas including the right middle frontal/the right precentral gyrus and the right cuneus/precuneus ($r = 0.65$, $p < 0.01$). There was no correlation between the other regions.

Table 1 Brain areas significantly activated during response inhibition

Area	BA	Cluster level		Voxel level		x	y	z
		p	k	p	T			
R superior temporal gyrus	22	0.000	1193	0.003	9.82	58	–42	18
R middle temporal gyrus	37			0.095	7.05	60	–52	8
R middle temporal gyrus	37			0.153	6.67	52	–60	10
R middle frontal gyrus	6	0.003	276	0.133	6.78	26	4	50
R precentral gyrus	9			0.983	4.42	44	12	38
R middle frontal gyrus	9	0.005	258	0.177	6.55	40	34	30
R middle frontal gyrus	46			0.288	6.15	48	30	18
R middle frontal gyrus	46			0.639	5.38	52	26	26
R cuneus	7	0.001	332	0.230	6.34	24	–76	40
R cuneus	19			0.292	6.14	34	–74	34
R precuneus	7			0.596	5.46	10	–66	52

The names of areas described above point to the peaks of activation within each cluster
p corrected p values for spatial extent (cluster level p value) and peak height (voxel level p value) of the activation: all areas exceeding the corrected cluster level threshold of 0.05 are displayed; *k* number of voxels in cluster; *T* t score; *x, y, z* localization according to the standard Talairach coordinates (in mm); *L* left; *R* right

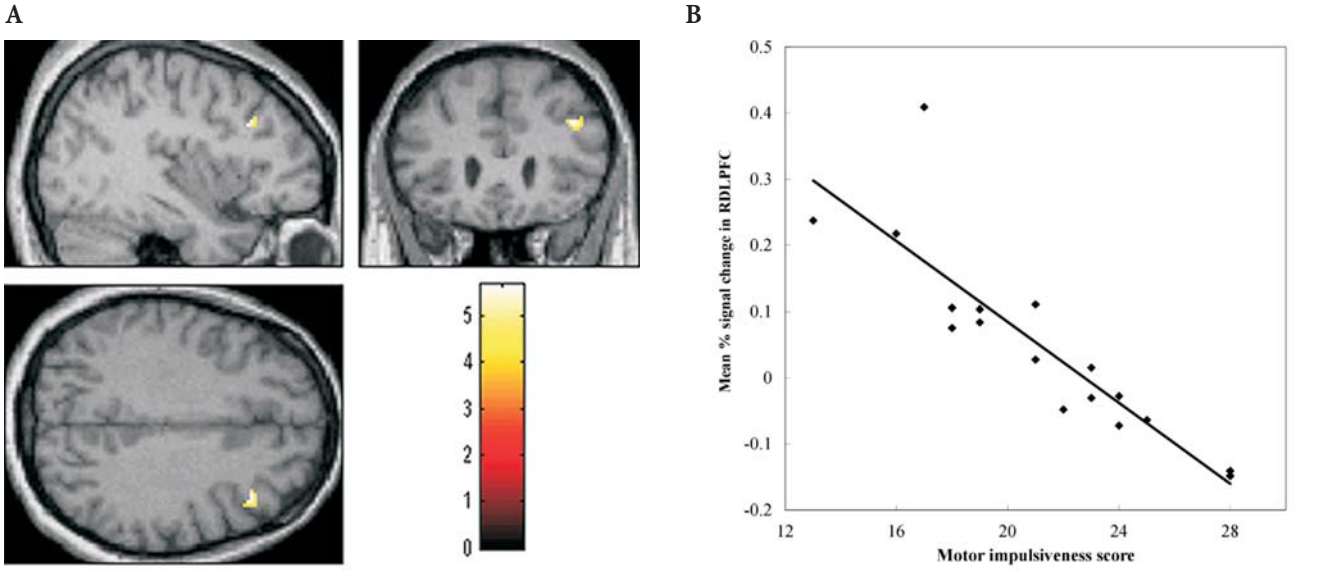

Fig. 2 **A** Statistical parametric maps of brain region (on the regression analysis for the 17 subjects) showing significant activation negatively associated with the motor-key score of BIS-11, within the areas activated during response inhibition, at a statistical threshold of $P < 0.05$ (uncorrected) on the single voxel level and $P < 0.05$ (corrected) on the cluster level. The region corresponds to the RDLPFC: x, y, z = 34, 22, 29; area 9; t-value = 5.66; 42 voxels. Clusters of activation are shown as through-projections onto representations of standard stereotactic space. *Sagittal* side view; *coronal* view from back; *transverse* view from above. **B** Correlation between mean percentage of signal change within the RDLPFC shown in Fig. 2A and the motor-key scores of BIS-11. The correlation coefficient is $r = –0.93$; $p < 0.01$

Discussion

In the present study, we examined the brain areas associated with impulsiveness as measured by BIS-11 in healthy volunteers. We have shown a significant negative correlation between the motor-key score of BIS-11 and the magnitude of activation in the right dorsolateral prefrontal cortex (RDLPFC) during the No-Go condition compared to that of the Go condition (i. e., as the motor-key score of BIS-11 increases, the signal intensity seen in the region including the RDLPFC decreases). These results suggest that the RDLPFC may play a more important role in response inhibition in motor inhibitory control than other brain regions.

We used BIS-11, a self-report measure, in the assessment of impulsiveness. This scale was designed to measure temperament, a long lasting characteristic of the personality of the subject. In addition, we can gather consistent information that is not affected by experimental methods or tasks. Our results illuminated the motor impulsiveness of BIS-11 as only a subscale, which has a significant association with the activation in the RDLPFC during response inhibition. Although the BIS-11 and its subscales have sufficient internal consistency reliability, other subscales did not show any association

between any brain regions activated during response inhibition. That may be because the Go/No-Go task we employed is a task emphasized on the motor response inhibition. Barratt (1994) reported that college students scored higher on average for motor impulsiveness than a mixed adult population and lower for cognitive impulsiveness, whereas a group of psychiatric inpatients scored high mainly on the non-planning impulsiveness [2]. This indicates that motor impulsiveness is more sensitive than other subscales of BIS (i. e. cognitive impulsiveness and non-planning impulsiveness) in young healthy persons and supports our result, which illuminated motor impulsiveness in our comparatively young (25.1 years old on average) healthy subjects.

In this study, brain activation associated with successful response inhibition was observed as a distributed network in the right hemisphere, which was consistent with the results of previous functional brain imaging studies that suggest right hemisphere regions, including the RDLPFC, the inferior parietal cortex and, medially, the anterior cingulate cortex (ACC), are especially important for inhibitory control [6, 7, 13, 20, 21, 27, 43]. In particular, the importance of the RDLPFC was emphasized after regression analysis. The RDLPFC is one of the most consistently activated areas in regard to inhibitory control, and is thought to participate in the active suppression of inappropriate movement and behavior. The right lateral prefrontal regions have been shown to be activated in countering proactive interference [7], set-shifting involving the inhibition of the previous rule in the Wisconsin Card Sorting task [27], response inhibition in the Stop paradigm [39, 43], suppression of imitative behavior [5], and a range of clinical disinhibition syndromes that follow right hemisphere damage [46, 48]. In addition to being involved in the suppression of movement and behavior, the RDLPFC is also associated with the voluntary suppression of a positive emotional reaction, such as sexual arousal [4], and the voluntary suppression of a negative emotion, such as sadness [29]. These facts indicate that the RDLPFC is a key structure involved in the variety of inhibitory control.

We did not observe any significant correlation between the performance data (i. e., the number of commission errors and omission errors, response time) and the magnitude of brain activation during response inhibition. This result is not consistent with the results of Garavan et al. (1999), which suggest that the faster a subject was in responding to the targets, the greater the signal intensity seen in the regions, including the right inferior frontal cluster and the left inferior parietal lobule cluster, during response inhibition [21]. Comparing our performance data with theirs, the percentage of commission errors and omission errors are almost the same. Therefore, it may be difficult to interpret the inconsistency simply as the task level of difficulty. Another possible interpretation is the difference of strategies in executing the task. The response time to targets and the accuracy of responses are conflicting natures in executing the Go/No-Go task. Both of these parameters may be sensitive and variable to the difference in strategies each subject used to emphasize the response time to targets or the accuracy of responses, when they are demanded to manage both. Actually, the mean response time to targets in our subjects (326 ms) was considerably shorter than that of the subjects in the other study (460 ms).

Casey et al. (1997) showed a significant negative correlation between the number of commission errors and the volume of activation in the orbital frontal gyrus [11]. Regrettably, our experimental conditions did not show a significant activation in the orbitofrontal cortex, as did other fMRI studies. This inconsistency may be due to the difference of methods employed. The correlation the other studies observed maybe reflected the developmental difference between adults and children, because those studies mixed adults and children as subjects in their experiment. In fact, those studies also showed that the volume of activation was significantly greater in children relative to adults when performing the No-Go condition of the task. However, the location of activation in the PFC was not different between the age groups. This observation may be due to susceptibility effects at the air-tissue interface in the perinasal sinuses, which renders orbitofrontal activation difficult to observe in fMRI. However, lesion studies in animals and in humans have traditionally implicated the orbitofrontal cortex in behavioral inhibition [19]. Therefore, we cannot exclude a potential role of the orbitofrontal cortex in inhibitory control based on fMRI data.

Liddle et al. (2001) [30] reported that the activation of ACC during No-Go trials was not substantially greater than that during Go trials under circumstances in which No-Go trials and Go trials were equally probable. In addition, they reported that the activation of ACC was related to decision formation and monitoring, rather than to response inhibition. These results may explain why our results have not shown activation in the ACC. We used a standard blocked design [11] in this study as a way to provide and maintain a high level of prepotent response. Randomly presenting an equal number of Go and No-Go stimuli would have eliminated a buildup of a prepotent response. In such a situation, the subjects were required to make and monitor decisions attentively during both conditions, which might result in little difference between the activation of the ACC during No-Go conditions and that during Go conditions.

In addition to those areas discussed above, we detected activities in other areas including the right middle frontal/the right precentral gyrus (frontal cortex) and the right cuneus/precuneus (parietal cortex). Moreover, a correlation was detected between both areas by analyzing the mean percentage signal changes in the regions during response inhibition. The observed activation in these two areas might be related to motor imagery, which is defined as the mental simulation of a motor act [12, 14], and is reported from neuroimaging studies to share neural substrates with those underlying motor execution [31, 40, 41]. The precentral sulcus at the level of middle

frontal gyrus and the posterior superior parietal/precuneus were reported to be activated more during motor imagery than the motor execution [23] and are thought to correspond to a 'negative motor area' where electrical stimulation causes a cessation of movement [32] because activity for inhibiting movement would be needed during motor imagery. Therefore, our observation that these areas are activated may be reasonable.

One of the most important issues of the present results is why high impulsive subjects perform as well as low impulsive subjects with less activity in the RDLPFC. It may be possible to explain this by the fact that a parametric manipulation of the ratio between Go and No-Go stimuli revealed the RDLPFC increases as inhibitory difficulty decreased, that is, as the relative numbers of No-Go stimuli increased, thereby diminishing response prepotency [10, 13]. That is thought to reflect the importance of maintaining relevant stimulus information against interference from competing non-target stimuli. Therefore, the high impulsive subjects with less activation in the RDLPFC may have less capacity left for response inhibition than that of less impulsive subjects. However, some fMRI studies concerning working memory showed an increased activity in the PFC with increasing memory loads, possibly due to a limited capacity of the system for controlled processing [25, 44]. Therefore, the relationship between the task difficulty and the activation in the PFC may depend on the tasks which require different processes of cognitive functions. Further studies are needed to clarify this issue.

One of the limitations of this study is that a block design was used for investigating motor response suppression. When employing block design, it is difficult to control for the difference in frequency of motor responses between blocks that differ in the proportion of Go and No-Go events. Casey et al. (1997) tried to avoid this difficulty by comparing the epochs containing Go and No-Go responses with two baseline conditions that contained only Go trials. One baseline was established from a frequency of Go trials that matched that in the No-Go condition (ensuring approximate matching of number of motor responses), while the other baseline was established with the total number of trials matching the No-Go condition (ensuring matching of the number of stimuli presented) [11]. Their results showed that the same areas were activated during No-Go conditions and Go conditions in both contrasts. Together, these results may support the validity of our study using the latter baseline. Another possible limitation is in measuring impulsiveness using questionnaires, which are subjective. Shortcomings on self-report measures include the need to rely on the honesty of the individuals completing the questionnaire.

Conclusion

We observed a negative correlation between the motor impulsiveness assessed by BIS-11 and the activation of the RDLPFC during response inhibition in healthy subjects. Our findings highlight the importance of the activity in the RDLPFC as the area most sensitive to the differences in individual motor impulsiveness, even in the healthy subjects. However, the role of the RDLPFC remains unclear, thus, further studies are needed.

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