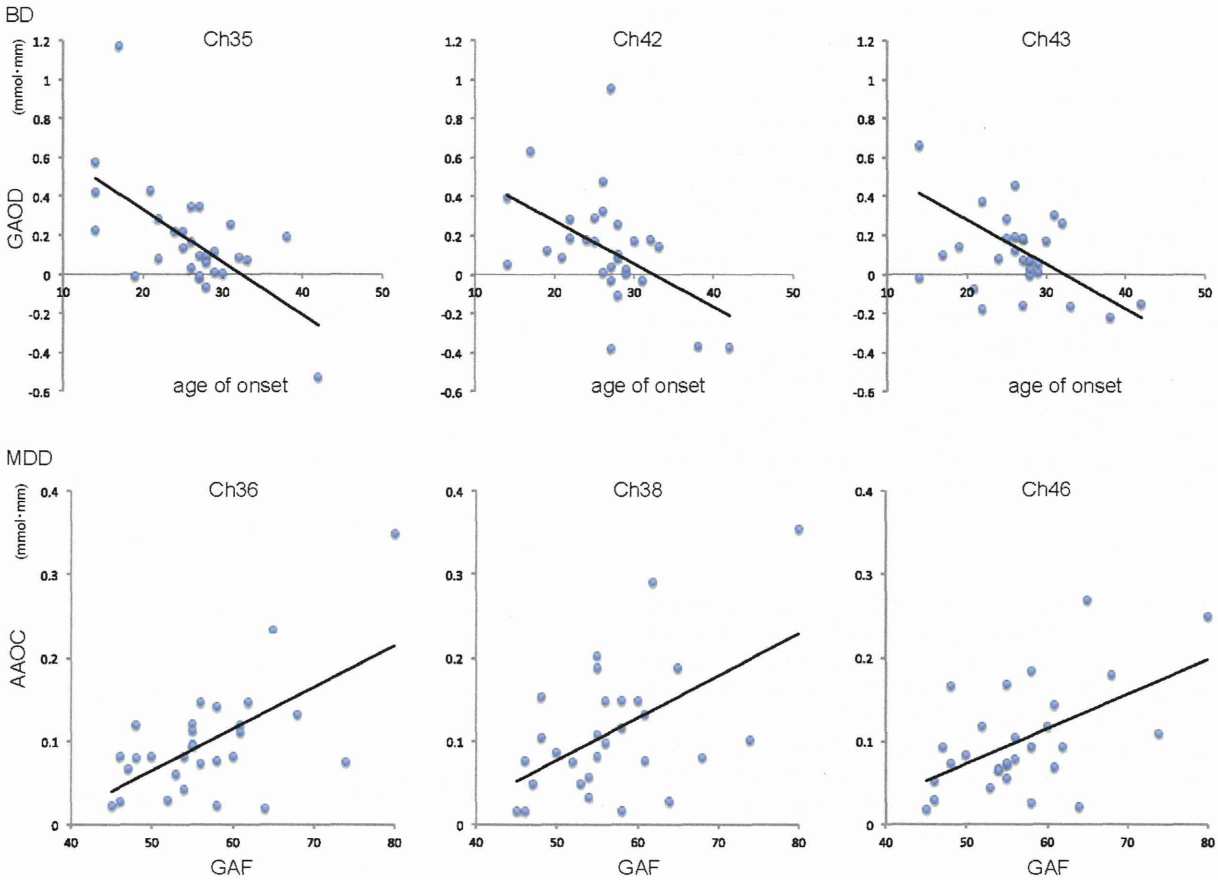

Fig. 6. Upper 3 figures (Ch35, Ch42, and Ch43): Significant negative correlation between the grand averaged [oxy-Hb] data (GAOD) during the conversation task of BD and age of onset. Lower 3 figures (Ch36, Ch38, and Ch46): Significant positive correlation between the AAOC data during the conversation task for MDD and GAF.

scores on the Social Adaptation Self-Evaluation Scale (SASS) in late-onset depression. Our results indicate that decreased AAOC in the right FPC may be reflected in the cognitive inflexibility of MDD, especially during face-to-face conversations. This may also be related to social adaptation through communication with others.

4.6. Limitations and future directions

The limitations of this study are as follows: (i) the results were mainly drawn from patients in the euthymic state, since few patients in depressive or hypomanic states were included; (ii) we were unable to investigate the correlation between NIRS measurements and psychotropic medication because we did not include drug-free patients, or patients taking a single drug; (iii) we did not evaluate neurocognitive function and intelligence quotient by other neuropsychological methods; therefore, we could not evaluate relationships between conversation performance and cognitive domains such as executive function or working memory; (iv) we could not identify an observable index of conversation that is more sensitive to the GAOD and AAOC. Future studies addressing these limitations are planned.

4.7. Conclusion

We used NIRS to investigate frontal lobe activation in MDD, BD, and NC participants during face-to-face conversations in situ, and demonstrated decreased activation and different temporal characteristics among the three groups. GAOD, which may reflect conversation situation-related function, was decreased in the left DLPFC and FPC in both MDD and BD groups. AAOC, which may reflect speech-related function, was decreased in the FPC in both the MDD and BD groups; this was shown more strongly in the right FPC for the MDD group. GAOD was negatively correlated with age of onset in BD, while AAOC was positively correlated with GAF in MDD. However, both continuous activation and rapid change may reflect the pathophysiological character of MDD and BD; in particular, the decrease of AAOC in the right FPC may be related to the impaired adaptive ability exhibited in MDD.

Conflict of interest

Authors have no conflicts of interest to declare.

Contributors

Masashi Suda and Yuichi Takei designed the tasks; Masashi Suda, Yuichi Takei, Yoshiyuki Aoyama, Kosuke Narita, Miho Yamaguchi, Minami Tagawa, Tomokazu Motegi, and Noriko Sakurai conducted the experiments and analyzed the data; and Yuichi Takei, Masashi Suda, and Masato Fukuda, wrote the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2014.06.009.

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Relationship of γ-aminobutyric acid and glutamate + glutamine concentrations in the perigenual anterior cingulate cortex with performance of Cambridge Gambling Task

Kazuyuki Fujihara [a], Kosuke Narita [a,*], Yusuke Suzuki [a], Yuichi Takei [a], Masashi Suda [a], Minami Tagawa [a], Koichi Ujita [b], Yuki Sakai [c], Jin Narumoto [c], Jamie Near [d], Masato Fukuda [a]

[a] Department of Psychiatry and Neuroscience, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan
[b] Department of Diagnostic Radiology and Nuclear Medicine, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan
[c] Department of Psychiatry, Graduate School of Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan
[d] Douglas Mental Health University Institute and Department of Psychiatry, McGill University, Montreal, QC, Canada

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ABSTRACT

The anterior cingulate cortex (ACC), consisting of the perigenual ACC (pgACC) and mid-ACC (i.e., affective and cognitive areas, respectively), plays a significant role in the performance of gambling tasks, which are used to measure decision-making behavior under conditions of risk. Although recent neuroimaging studies have suggested that the γ-aminobutyric acid (GABA) concentration in the pgACC is associated with decision-making behavior, knowledge regarding the relationship of GABA concentrations in subdivisions of the ACC with gambling task performance is still limited. The aim of our magnetic resonance spectroscopy study is to investigate in 20 healthy males the relationship of concentrations of GABA and glutamate + glutamine (Glx) in the pgACC, mid-ACC, and occipital cortex (OC) with multiple indexes of decision-making behavior under conditions of risk, using the Cambridge Gambling Task (CGT). The GABA/creatine (Cr) ratio in the pgACC negatively correlated with delay aversion score, which corresponds to the impulsivity index. The Glx/Cr ratio in the pgACC negatively correlated with risk adjustment score, which is reported to reflect the ability to change the amount of the bet depending on the probability of winning or losing. The scores of CGT did not significantly correlate with the GABA/Cr or Glx/Cr ratio in the mid-ACC or OC. Results of this study suggest that in the pgACC, but not in the mid-ACC or OC, GABA and Glx concentrations play a distinct role in regulating impulsiveness and risk probability during decision-making behavior under conditions of risk, respectively.

Introduction

Gambling tasks in a laboratory are used to measure decision-making behavior under conditions of risk, and these require matching the subjective values of potential wins and losses against the probability of their occurrence (Studer et al., 2012). Abnormal betting in gambling tasks characterized by impairments of decision-making behavior, such as an increasing level of risk taking or impulsivity, has been observed in a number of psychiatric disorders, such as pathological gambling (Grant et al., 2011; Cavedini et al., 2002), substance dependence (Grant et al., 2000; Adinoff et al., 2003; Bolla et al., 2003; Le Berre et al., 2014; Ersche et al., 2005), dementia (Rahman et al., 1999), attention-deficit/hyperactivity disorder (DeVito et al., 2008), bipolar disorder (Linke et al., 2013; McIntyre et al., 2007; Chandler et al., 2009), and schizophrenia (Shurman et al., 2005; Larquet et al., 2010). Thus, elucidating the neural basis of the processing of gambling tasks in vivo is important to our understanding of the pathophysiological mechanisms underlying impairments of decision-making behavior associated with these psychiatric illnesses. A recent line of evidence has revealed that the anterior cingulate cortex (ACC), as well as the ventromedial prefrontal cortex, orbitofrontal cortex, and insula, is one of the brain regions responsible for processing during a gambling task (Clark et al., 2008; Manes et al., 2002). In previous functional magnetic resonance imaging (MRI) studies using the Iowa gambling task or simple card gambling tasks, the performance of these tasks is positively associated with blood-oxygenation-level-dependent (BOLD) activation in the medial frontal cortex including the ACC in healthy volunteers (Fukui et al., 2005; Bechara et al., 1994; Li et al., 2010; Rudorf et al., 2012). Moreover, Rogers et al.(2004) reported that healthy volunteers show BOLD activation in the ACC and superior frontal gyrus during the original gambling task, the paradigm of which involves making one out of two available choices, consisting of a 50% chance of winning and a 50% chance of losing.

* Corresponding author at: Department of Psychiatry and Neuroscience, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan. Fax: +81 776 61 8136.
E-mail address: knarita.med.gunma.u@gmail.com (K. Narita).

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Previous functional and anatomical lines of evidence reveal that the ACC consists of two major parts in humans, the perigenual ACC (pgACC) and mid-ACC. The pgACC is predominantly involved in affective control and is anatomically connected to the amygdala, hippocampus, hypothalamus, insula, nucleus accumbens, and orbitofrontal cortex. In contrast, the mid-ACC, which significantly contributes to cognitive function, is connected to the dorsolateral prefrontal cortex (Bush et al., 2000; Shackman et al., 2011). Recently, two notable neuroimaging studies by magnetic resonance spectroscopy (MRS) focusing on the pgACC have shown a significant association between γ-aminobutyric acid (GABA) concentration and the performance of decision making or the level of impulsivity. Firstly, Jocham et al. (2012) described that, in healthy males, the GABA concentration in the medial prefrontal cortex including the pgACC positively correlates with the performance of a task with two choices consisting of "high" and "low" rewards. Secondly, Silveri et al. (2013) reported that the GABA concentration in the pgACC negatively correlates with impulsivity estimated by self-report measurement, i.e., Barratt Impulsiveness Scale-11 (Patton et al., 1995), in healthy adolescents and adults. GABA acts as a major inhibitory neurotransmitter in the central nervous system. Thus, the above-mentioned two MRS studies of healthy subjects suggest that GABAergic abnormality in the pgACC can affect decision-making behavior through failure in the accuracy of choice for rewards or in the control of impulsivity.

In patients with bipolar disorder and schizophrenia, recent MRS studies have shown the alterations in the concentrations of metabolites, such as GABA and glutamate + glutamine (Glx), in the pgACC (Frye et al., 2007; Kegeles et al., 2012). The Glx concentration detected by MRS is considered to be very likely related to excitatory neurotransmission (Bauer et al., 2013). Because other lines of evidence suggest that the above-mentioned psychiatric patients also show abnormalities of gambling task performance (Chandler et al., 2009; Shurman et al., 2005; Larquet et al., 2010), a better understanding of the pathophysiological mechanisms underlying abnormalities of decision making under conditions of risk in such patients can be expected by further MRS study focusing on the ACC using gambling tasks. However, there are no previous studies of the relationship between the concentrations of metabolites in comprehensive areas of the ACC, i.e., the pgACC and mid-ACC, and gambling task performance, despite some neuroimaging studies suggesting that the mid-ACC, as well as the pgACC, contributes to processing during a gambling task (Engelmann and Tamir, 2009).

In this MRS study, using a cross-sectional design, we examined the relationship of the concentrations of GABA and Glx in the pgACC, mid-ACC, and occipital cortex (OC) with decision-making behavior under conditions of risk using the Cambridge Gambling Task (CGT) in 20 healthy males (Morris et al., 1987). We hypothesized that the concentration of GABA negatively correlates with impulsivity specifically in the pgACC. The mid-ACC and OC were included as the control voxel. MEscher-GArwood Point RESolved Spectroscopy (MEGA-PRESS) was performed using the MRS sequence, which enables simultaneous detection of GABA and Glx (Mescher et al., 1998).

Materials and methods

Subjects

Twenty healthy males (mean age, 27.3 ± 7.6 years; age range, 16–40 years) were recruited from Gunma Prefecture, Japan. Because the menstrual cycle might affect the concentration of GABA in females (Silveri et al., 2013; Epperson et al., 2006), we enrolled only males as study subjects. All subjects had no history of significant medical illness (e.g., neurological, cardiovascular, or endocrine disease), head trauma, personality disorder, or significant psychiatric disorder (e.g., mood disorders, anxiety disorders, adjustment disorders, or schizophrenia), chronic alcoholism or substance abuse, pathological gambling, or current chronic medication. In addition, they had no familial history of psychiatric illness within first-degree relatives. Furthermore, all the subjects enrolled in this study were right-handed as assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). To exclude the subjects with past or present major mental disorders or personality disorders, the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1996) and that for Axis II Disorders (First et al., 1997) were used. The study protocol was approved by the Ethics Committee of the Gunma University Graduate School of Medicine. All the participants provided written informed consent before the experiment. A summary of demographic data and neuropsychological assessment results is shown in Table 1.

Neuropsychological assessments

The intelligence quotient (IQ) of each subject was estimated using the Japanese version of the National Adult Reading Test (JART) (Matsuoka et al., 2006; Nelson, 1982). The subjects' socioeconomic status (SES) and parents' SES were assessed using the Hollingshead scale (Hollingshead, 1957). Furthermore, the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993) was also carried out to determine the possible effect of alcohol intake on GABA and Glx concentrations.

The Cambridge neuropsychological test automated battery [CANTAB (Morris et al., 1987); Cambridge Cognition Ltd., Cambridge, United Kingdom] administered to each subject of this study consisted of the following: the Spatial Recognition Memory (SRM) test of visual spatial memory in a two-choice forced discrimination paradigm; the Paired Associate Learning (PAL) test for the assessment of a simple visual pattern and visuospatial associative learning; the Rapid Visual Information Processing (RVIP) test, which is a visual continuous performance task using digits instead of letters; and the CGT for assessing decision-making behavior under conditions of risk.

In the CGT, the subject is presented with a row of ten blue or red boxes, the ratio of which is determined stochastically in each trial. The subject is informed that the computer has hidden a yellow token in one of those ten boxes. After guessing whether a yellow token is hidden in a red box or a blue box, the subject is asked to stake a proportion

Table 1
Demographic characteristics of study subjects.

	Males
Number	20
Age (y)	27.2 ± 7.5
Education (y)	15.0 ± 1.8
SES score (point)	2.0 ± .7
Parental SES score (point)	2.9 ± .8
JART—predicted full-scale IQ (point)	110.4 ± 8.4
Alcohol use disorders identification test (point)	6.7 ± 5.8
Cambridge Neuropsychological Test Automated Battery	
Spatial recognition memory (percent correct)	88.30 ± 8.00
Spatial recognition memory (total errors)	1.00 ± 1.40
Rapid visual information processing (A')	.96 ± .05
Cambridge Gamble Task (A.U.)	
Delay aversion	.17 ± .17
Risk adjustment	1.68 ± 1.07
Risk taking	.49 ± .15
MRS data, corrected for gray matter volume within VOI (A.U.)	
Perigenual anterior cingulate cortex	
GM-corrected GABA/Cr	.166 ± .062
GM-corrected Glx/Cr	.106 ± .024
Mid-anterior cingulate cortex	
GM-corrected GABA/Cr	.264 ± .070
GM-corrected Glx/Cr	.139 ± .036
Occipital cortex	
GM-corrected GABA/Cr	.398 ± .132
GM-corrected Glx/Cr	.136 ± .099

SES, socioeconomic status; JART, Japanese version of National Adult Reading Test; A', signal detection measures of accuracy, MRS, magnetic resonance spectroscopy; A.U., arbitrary unit; VOI, voxel of interest; GABA,γ-aminobutyric acid; Glx, glutamate + glutamine; Cr, creatine. GM, gray matter. GM-corrected GABA/Cr or Glx/Cr means GABA/Cr or Glx/Cr corrected for the relative volume of the gary matter within each voxel of interest. Mean ± SD.

(i.e., 5%, 25%, 50%, 75%, or 95%) of their points on that decision. These stake options are presented in an ascending or descending order (Clark et al., 2008). As parameters of CGT, the following three outcome measures were used in this study. The first is delay aversion, indicated as "impulsivity index", which is calculated as the difference in percent bet when presented with the options in descending versus ascending order. When the subject tends to wage bets at a larger proportion of points when the options are presented in descending order rather than ascending order, the delay aversion score would be larger (Newcombe et al., 2011). The second is risk adjustment, which is calculated as [2 × (% bet 9:1) + (% bet 8:2) − (% bet 7:3) − 2 × (% bet 6:4)] ÷ (average % bet). Here, "% bet A:B" represents the proportion of current points that the subject bets on when the ratio of the major color to the minor color is A:B. A higher risk adjustment score indicates that the subject changes the wager depending on the probability of winning. The third is risk taking, which is the average proportion of the current total points that the subject bets in the trials in which he chooses a major color.

T1-weighted anatomical imaging and MRS acquisition

Brain MRI and MRS were performed using Siemens 3-T Trio with a 12-channel head coil (Siemens, Erlangen, Germany) in Gunma University Hospital. High-resolution T1-weighted anatomical images [magnetization-prepared rapid acquisition with gradient echo (MP-RAGE) sequence] were acquired to determine the location of the voxel of interest (VOI) during MRS scanning and to calculate the gray matter volume within that VOI. Imaging parameters were as follows: repetition time = 2000 ms; echo time = 2 ms; inversion time = 990 ms; flip angle = 9 degrees; field of view = 256 mm × 256 mm; matrix size = 256 × 256; voxel size = 1 × 1 × 1 mm^3. We used the vendor-provided shimming tool that is standard to the Siemens Trio MRI system. Specifically, this involves the acquisition of a whole-brain fieldmap, followed by calculation of the required shim currents to shim the specific region of interest. Both first- and second-order shim adjustments were performed, as is the default setting in the Siemens environment.

The edited GABA and Glx MRS spectra were acquired by the MEGA-PRESS method as previously described (Mescher et al., 1998). In the direction of the excitation pulse (bandwidth = 3708 Hz, selective in the left-right direction), the chemical shift displacement between GABA and Glx was 0.75 mm. In the directions of the refocusing pulses (bandwidth = 1106 Hz, selective in the anterior–posterior direction and in the superior–inferior direction), the chemical shift displacement between GABA and Glx was 1.67 mm. The VOI in MRS (30 × 20 × 20 mm^3) was placed in the pgACC, mid-ACC, and OC. The acquisition parameters were as follows: TR = 2400 ms; TE = 68 ms; average numbers = 512 for the pgACC and mid-ACC, and 256 for OC. The VOI in the pgACC was defined as follows. After drawing "line a" exactly on the rostral margin of the corpus callosum as the perpendicular axis to the anterior commissure–posterior comissure (AC–PC) line (see Fig. 1A), the VOI in the pgACC was set along "line a" and on the inferoposterior corner located at the rostral edge of the genu. The VOI in the mid-ACC was placed directly above the superior surface of the corpus callosum together with the posterior margin of the VOI aligned along "line b", which is the perpendicular axis through AC to the AC–PC line (see Fig. 1A). The OC voxel was placed with the inferior edge of the voxel aligned with the AC–PC line.

We measured the full-width at half-maximum (FWHM) of *N*-acetyl asparate (NAA) peaks in the MEGA-PRESS spectra to determine the quality of shimming. The means ± standard deviations (SD) of each region were 10.612 ± 3.583 Hz in pgACC, 8.259 ± 3.093 Hz in mid-ACC, and 5.683 ± 0.622 Hz in OC. We excluded the samples whose the FWHM of NAA was broad (i.e., FWHM > mean ± 2 SD). Although data from the pgACC and OC were successfully collected from all the participants, that from the mid-ACC of one participant was excluded from the analysis because the FWHM of NAA was broader than the cut-off value. In addition, we evaluated the motion artifact by visual inspection of superimposed spectra from all the excitations during a scanning of MEGA-PRESS. As a result, two samples of mid-ACC were also excluded owing to motion artifacts.

Processing and analysis of MRS data

Prior to signal averaging, each scan was frequency- and phase-aligned using an in-house program written in MATLAB (MathWorks, Natick, MA, USA) to minimize the effects of frequency and phase drifts, and motion-corrupted averages were removed as described previously (Near et al., 2013). Averaged difference spectra and sum spectra were then line-broadened using a 5-Hz Lorentzian filter, and zero-order phase corrections were applied manually to ensure upright peaks.

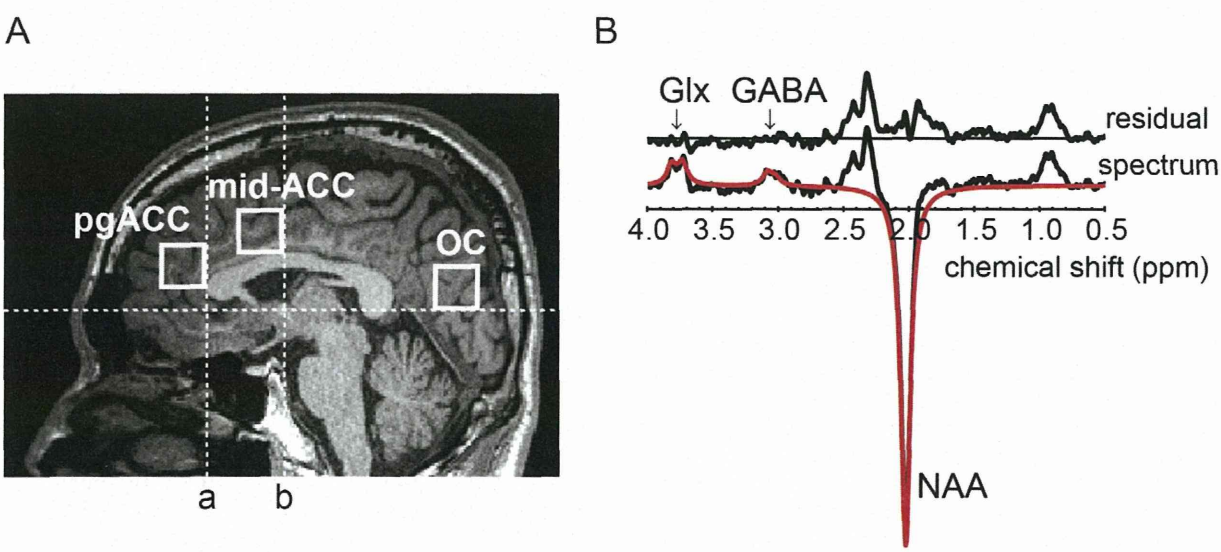

Fig. 1. Magnetic resonance spectroscopy (MRS) with MEscher–GArwood SPin-ECho full-Intensity Acquired Localized (MEGA–SPECIAL) method. The voxels of interest (30 × 20 × 20 mm^3) in MRS, which were located on the perigenual anterior cingulate cortex (pgACC), mid-ACC, and occipital cortex (OC), are shown in Fig. 1A; "line a" is placed exactly on the rostral margin of the corpus callosum as the perpendicular axis to the anterior commissure–posterior commissure (AC–PC) line. "Line b" is drawn as the perpendicular axis through the anterior commissure to the AC–PC line. The edited spectrum (i.e., black line) and fitted curve (i.e., red line), which were obtained for the signal quantification of γ-aminobutyric acid, glutamate + glutamine and creatine concentrations, are shown in Fig. 1B.

First-order phase corrections were also applied manually in some cases because the first point in the fit did not always correspond exactly to the top of the echo. GABA and Glx signals from the difference spectra and creatine (Cr) signals from the sum spectra were quantified using the AMARES package provided in the jMRUI software (Vanhamme et al., 2001; Naressi et al., 2001). GABA, Glx, and Cr were modeled as a triplet, a doublet, and a singlet of Lorentzian peaks, respectively. Because the editing efficacy for Glx has not been determined in the current sequence, Glx signals are reported in an arbitrary unit value.

The obtained T1-weighted anatomical images were segmented into the gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using FAST (FMRIB's automated segmentation tool) (Zhang et al., 2001) in FSL software (available from http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) (Zhang et al., 2001; Smith et al., 2004; Woolrich et al., 2009; Jenkinson et al., 2012) to calculate the relative volume of each tissue within the VOI in MRS.

Statistical analyses

The metabolite ratios presented in the results section of this study, i.e., GABA/Cr and Glx/Cr, as well as GM-corrected GABA/Cr and GM-corrected Glx/Cr, which were corrected for the relative volume of the GM within each VOI in MRS in accordance with a previous study (Jocham et al., 2012). Because GABA/Cr and Glx/Cr correlate to each other as reported by Jocham et al. (2012), we also included both metabolites ratios in the partial correlation analysis for removing each other's effect. To assess the relationship among demographic characteristics, CANTAB scores, and metabolite ratios in MRS (i.e., GABA/Cr and Glx/Cr), Spearman's rho correlation test and partial rank correlation with adjustment for confounding factors (age and AUDIT score) were performed. On the basis of Q–Q plot inspection (Supplementary Fig. S1), we carried out nonparametric analysis, i.e., Spearman's correlation test, because of the possible lack of normality in some parameters, i.e., GABA/Cr. In addition, we also performed regression analysis, in accordance with a previous report (Yildiz et al., 2014). A p-value of <0.05 was set as statistically significant. We calculated the 95% confidence interval (CI) of Spearman's rho by bootstrapping for significant correlation. The number of replicates for bootstrap was set at 20,000. For analysis of the correlation between the two metabolite ratios (GABA/Cr and Glx/Cr) and three subscales of the CGT in each of the three VOIs (pgACC, mid-ACC, and OC), we corrected $18 \times p$-values by Bonferroni correction. All the statistical analyses were carried out using R software (available from http://www.r-project.org/) (R Development Core Team, 2011).

Results

The predicted IQs were higher than 90 in all the participants (mean ± SD = 110.4 ± 8.4) (see Table 1). Spearman's rho correlation test showed that both metabolite ratios (GM-corrected GABA/Cr and GM-corrected Glx/Cr) in all VOIs did not significantly correlate with age, education years, SES score, parental SES score, predicted IQ, or ADULT score. Although the GM-corrected Glx/Cr in the mid-ACC, but not in the pgACC and OC, showed a significant correlation with SRM score ($r = 0.488$, $p = 0.047$), this significant correlation did not persist after adjustment for confounding factors. The GM-corrected GABA/Cr in all VOIs showed no significant correlation with SRM score. Moreover, both metabolite ratios in all VOIs did not correlate with any scores of memory or attentive function measurement, i.e., PAL or RVIP (Supplementary Table S1). Considering that the concentrations of Cr in all VOIs did not significantly correlate with CGT scores, we used Cr-normalized values (GABA/Cr and Glx/Cr) for further analysis.

GABA/Cr and CGT scores

Spearman's correlation showed a significant negative correlation between the GM-corrected GABA/Cr in the pgACC and delay aversion score ($r = -0.652$, $p = 0.0018$, 95% CI calculated by bootstrapping = −0.842 to −0.332) (see Supplementary Table S1). This significant correlation remained after adjustment for confounding factors and Bonferroni correction in multiple comparisons ($r = -0.686$, $p = 0.0002$; Bonferroni-adjusted $p = 0.0046$). On the other hand, the GM-corrected GABA/Cr in the mid-ACC and OC did not correlate with delay aversion score. Moreover, the GM-corrected GABA/Cr in all the VOIs, i.e., the pgACC, mid-ACC, and OC, did not correlate with the score of risk adjustment or risk taking.

In the regression analysis, both the raw-GABA/Cr and GM-corrected GABA/Cr in the pgACC could also predict delay aversion score (raw GABA/Cr, $\beta = -0.5743$, $t = -2.976$, $p = 0.0081$; GM-corrected GABA/Cr, $\beta = -0.5892$, $t = 3.094$, $p = 0.0063$) (see Fig. 2). To control further for possible effects of GM, WM and CSF fractions, we used these fractions in separate regression models for raw GABA/Cr similarly to Yildiz et al. (2014). All these models revealed that neither GM, WM, nor CSF explained further variance in the models ($|\beta| < 0.1118$, $|t| < 0.758$, $p > 0.4589$). Finally, we added Glx/Cr to the regression analysis as a covariate. This regression model showed that only GABA/Cr has a predictive effect ($\beta = -0.6955$, $t = -3.083$, $p = 0.0067$), not Glx/Cr ($\beta = 0.2328$, $t = 1.032$, $p = 0.3165$), on delay aversion in the pgACC.

Glx/Cr and CGT scores

Spearman's correlation showed a significant negative correlation between the GM-corrected Glx/Cr ratio in the pgACC and risk adjustment score ($r = -0.579$, $p = 0.0075$, 95% CI calculated by bootstrapping = −0.844 to −0.324) (see Supplementary Table S1), and this significant correlation remained after adjustment for confounding factors and Bonferroni correction for multiple comparisons ($r = -0.629$, $p = 0.0017$; Bonferroni adjusted $p = 0.0312$). On the other hand, the GM-corrected Glx/Cr ratio in the mid-ACC and OC did not correlate with risk adjustment score (see Supplementary Table S1). Moreover, the GM-corrected Glx/Cr ratio in all the VOIs, i.e., the pgACC, mid-ACC, and OC, did not correlate with the score of delay aversion or risk taking.

In the regression analysis, both the raw-Glx/Cr and GM-corrected GABA/Cr in the pgACC could also predict risk adjustment score (raw Glx/Cr, $\beta = -0.5751$, $t = -2.983$, $p = 0.0080$; GM-corrected Glx/Cr, $\beta = -0.5892$, $t = -3.094$, $p = 0.0063$) (see Fig. 3). Then, analysis using separate regression models to control further for the possible effects of GM, WM and CSF fractions was conducted. All these models revealed that neither GM, WM, nor CSF explained further variance in the models ($|\beta| < 0.3424$, $|t| < 1.899$, $p > 0.0747$). Finally, we added GABA/Cr to the regression analysis as a covariate. This regression model showed that only Glx/Cr has a predictive effect ($\beta = -0.7359$, $t = -3.345$, $p = 0.0038$), not GABA/Cr ($\beta = 0.3088$, $t = 1.404$, $p = 0.1783$), on risk adjustment.

Discussion

In this study, we found that the GABA/Cr ratio in the pgACC negatively correlated with delay aversion score. Furthermore, the Glx/Cr ratio negatively correlated with risk adjustment score. On the other hand, no significant relationships were found between risk taking score and the GABA/Cr or Glx/Cr ratio in the pgACC. Moreover, there were no significant correlations between all CGT scores and the GABA/Cr or Glx/Cr ratio in the mid-ACC or OC.

A higher delay aversion score has been reported to reflect the existence of increasing level of impulsivity (Newcombe et al., 2011; Deakin et al., 2004). Thus, the significant negative correlation between the GABA/Cr ratio in the pgACC, but not in the mid-ACC or OC, and delay aversion score observed in this study suggests that the

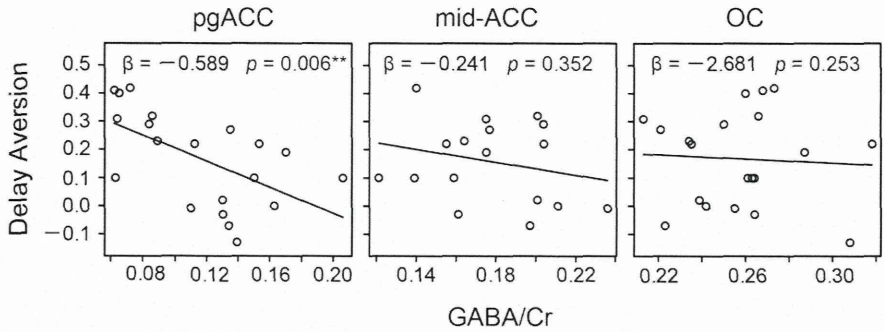

Fig. 2. Scatter plots showing correlation between delay aversion score of Cambridge gambling task and γ-aminobutyric acid (GABA) to creatine (Cr) ratio in perigenual anterior cingulate cortex (pgACC), mid-ACC, and occipital cortex (OC).

lower GABA concentration in the pgACC contributes to the impaired impulsiveness control during the CGT. Consistently, the pgACC is one of the key regions involved in impulsiveness control (Clark et al., 2008; Manes et al., 2002). In addition, previous MRS research revealed that the adolescent subjects with low GABA concentrations in the pgACC are likely to show high motor, nonplanning, and total impulsivity levels, as measured using a self-reported scale, Barratt Impulsiveness Scale-11 (Silveri et al., 2013). In the mid-ACC and OC, no significant association between GABA concentration and delay aversion score was observed in this study, which is consistent with the result of Boy et al. (2011) showing no significant association between GABA concentration in the mid-ACC and impulsivity level, as measured using the self-reported UPPS impulsive behavior scale (Whiteside and Lynam, 2001). Taking our above-mentioned results together with those of previous MRS studies using self-reported scales, the GABAergic system in the pgACC, which is an affective area of the ACC, might play an important role in impulsiveness control during decision-making processes under condition of risk, than those in the mid-ACC, which is a cognitive area of the ACC, and OC, which is the visual cortex region. Interestingly, Boy et al. (2011) also reported that the GABA concentration in right dorsolateral prefrontal cortex, which we were unable to estimate in this study, negatively correlated with above-mentioned self-reported impulsivity. Further research focusing on the association between the GABA concentration in the dorsolateral prefrontal cortex and scores of CGT will be required.

Another main finding of our study is the negative correlation between risk adjustment score and Glx concentration in the pgACC. The risk adjustment score of the CGT, which reflects the ability to change the amount of the bet depending on the probability of winning or losing, has been reported to be significantly decreased in patients with damage to the medial prefrontal cortex including the pgACC, as well as the orbitofrontal cortex, dorsolateral prefrontal cortex or insula, compared with healthy controls (Clark et al., 2008; Manes et al., 2002; Studer et al., 2013). Glx concentration is very likely related to excitatory neurotransmission, because glutamate is considered to be the major component of the Glx signal (Bauer et al., 2013). Interestingly, some MRS studies have shown a high Glx concentration in the pgACC in the subjects with addictive behavior or disability in reward-associated decision making. In alcohol-dependent patients, the Glx concentration in the pgACC is significantly positively associated with the score of obsessive compulsive drinking scale (Bauer et al., 2013; Anton et al., 1996). In healthy males, the Glx concentration in the ventromedial prefrontal cortex including the ACC is reported to negatively correlate with the accuracy of decisions in two choices consisting of "high" and "low" rewards (Jocham et al., 2012). Thus, a negative correlation between risk adjustment score and Glx concentration in the pgACC observed in this study suggests that the abnormality of the glutamatergic system, i.e., high Glx concentration, in the pgACC likely induces a disability of optimizing the bet during the CGT.

More recent lines of evidence suggest that striatal GABA concentrations strongly modulate response inhibition processes occurring in frontostriatal networks. Quetscher et al. (2014) have reported that a higher GABA concentration in the right striatum is related to a better response inhibition in the Go/NoGo task and that striatal GABA concentration is associated with the neural synchronization level of the theta-frequency band at approximately 5 Hz in the frontal lobe area. It is well known that the ACC and striatum are anatomically connected and are part of the neural circuit related to decision making (Tekin and Cummings, 2002). Furthermore, the striatal GABAergic medium spiny neurons play an important role in information encoding and behavioral control (Adler et al., 2013). Thus, MRS research to estimate the GABA concentrations in the striatum and ACC to reveal the interactions of the GABAergic system in the striatum and ACC associated with impulsivity control in frontostriatal networks should be conducted in the future.

In addition to the small sample size, there are some limitations of this study as follows. We were unable to obtain a causal effect of GABA or Glx concentration in the regional brain areas on the performance of the CGT, because our cross-sectional design did not include a load test for those

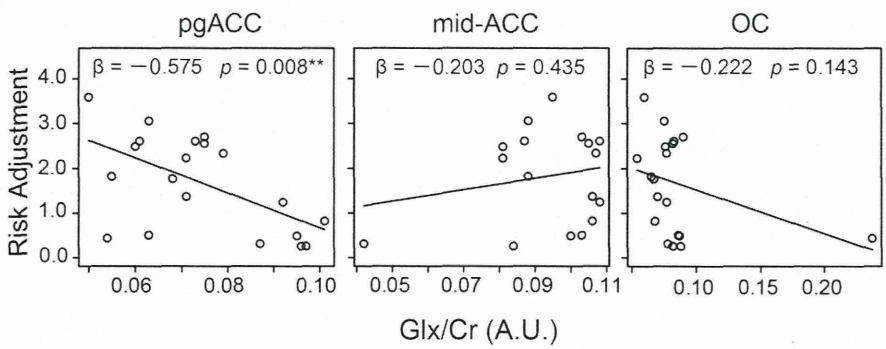

Fig. 3. Scatter plots showing correlation between risk adjustment score of Cambridge gambling task and glutamate + glutamine (Glx) to creatine (Cr) ratio in perigenual anterior cingulate cortex (pgACC), mid-ACC, and occipital cortex (OC).

metabolites. Additionally, only males were enrolled as study subjects; there was a lack of data on females because of the effects of the menstrual cycle on GABA concentration (Silveri et al., 2013; Epperson et al., 2006). Further studies with a larger sample size, including female subjects controlled for the effect of menstrual cycle, should be conducted. Moreover, additional investigations with comparison between psychiatric patients with mood disorder or schizophrenia and healthy controls can help improve our understanding of pathophysiological mechanisms underlying abnormalities of gambling task performance in these patients (Chandler et al., 2009; Shurman et al., 2005; Larquet et al., 2010).

In conclusion, this MRS study with the CGT showed that in the pgACC, but not in the mid-ACC or OC, the GABA concentration inversely correlated with delay aversion score, which can reflect the level of impulsivity. Moreover, the Glx concentration in the pgACC inversely correlated with risk adjustment score, which can be considered as the ability to optimize the bet, suggesting that the GABAergic and glutamatergic systems in the pgACC have different effects on decision-making processes under conditions of risk. The finding of this study should contribute to improving our understanding of the associations of excitatory and inhibitory systems with decision-making processes under conditions of risk in humans.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.01.014.

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Concurrent fNIRS-fMRI measurement to validate a method for separating deep and shallow fNIRS signals by using multidistance optodes

Tsukasa Funane,[a,*] Hiroki Sato,[a] Noriaki Yahata,[b] Ryu Takizawa,[c,d] Yukika Nishimura,[c] Akihide Kinoshita,[c] Takusige Katura,[a] Hirokazu Atsumori,[a] Masato Fukuda,[e] Kiyoto Kasai,[c] Hideaki Koizumi,[a] and Masashi Kiguchi[a]
[a]Hitachi, Ltd., Central Research Laboratory, Hatoyama, Saitama 350-0395, Japan
[b]The University of Tokyo, Graduate School of Medicine, Department of Youth Mental Health, Bunkyo-ku, Tokyo 113-8655, Japan
[c]The University of Tokyo, Graduate School of Medicine, Department of Neuropsychiatry, Bunkyo-ku, Tokyo 113-8655, Japan
[d]King's College London, Institute of Psychiatry, MRC Social, Genetic and Developmental Psychiatry Centre, London, SE5 8AF, United Kingdom
[e]Gunma University Graduate School of Medicine, Department of Psychiatry and Human Behavior, Maebashi, Gunma 371-8511, Japan

Abstract. It has been reported that a functional near-infrared spectroscopy (fNIRS) signal can be contaminated by extracerebral contributions. Many algorithms using multidistance separations to address this issue have been proposed, but their spatial separation performance has rarely been validated with simultaneous measurements of fNIRS and functional magnetic resonance imaging (fMRI). We previously proposed a method for discriminating between deep and shallow contributions in fNIRS signals, referred to as the multidistance independent component analysis (MD-ICA) method. In this study, to validate the MD-ICA method from the spatial aspect, multidistance fNIRS, fMRI, and laser-Doppler-flowmetry signals were simultaneously obtained for 12 healthy adult males during three tasks. The fNIRS signal was separated into deep and shallow signals by using the MD-ICA method, and the correlation between the waveforms of the separated fNIRS signals and the gray matter blood oxygenation level–dependent signals was analyzed. A three-way analysis of variance (signal depth × Hb kind × task) indicated that the main effect of fNIRS signal depth on the correlation is significant [$F(1,1286) = 5.34$, $p < 0.05$]. This result indicates that the MD-ICA method successfully separates fNIRS signals into spatially deep and shallow signals, and the accuracy and reliability of the fNIRS signal will be improved with the method. [DOI: 10.1117/1.NPh.XX.XX.XXXXXX]

Keywords: functional near-infrared spectroscopy; functional magnetic resonance imaging; laser Doppler flowmetry; verbal-fluency task; working memory; finger tapping.

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1 Introduction

Functional near-infrared spectroscopy (fNIRS) measures the changes in cerebral hemodynamics and oxygenation by radiating weak visible or near-infrared light into the head and detecting the light reflected back (scattered) from another position.[1–5] fNIRS has been applied to obtain two-dimensional topographical images of the changes in brain hemodynamics and oxygenation.[6,7]

All over the world, fNIRS systems have been used in more and more situations,[8] such as in neuroimaging research[9,10] and medical purposes,[11–14] especially for measuring the brain activity of infants and children[15–20] and for creating wearable equipment,[21,22] because they have a high level of safety[23,24] and require few constraints.

One of the limitations of fNIRS is the potential effect of the extracerebral tissue on the signal. It was reported that an fNIRS signal can be contaminated by extracerebral signals.[25–29] It has also been reported that the regional cerebral oxygen saturation is affected by extracranial contamination.[30,31]

Another issue concerning extracerebral effects is the interference of systemic hemodynamics on fNIRS signals.[32,33] This is often referred to as broadly distributed signals caused by heart rate, blood pressure, and respiration. In other words, it is attributed to the effect of measuring systemically circulating blood. Systemic interference is included both in extracerebral and cerebral signals, so a signal originating from cerebral tissue may include a systemic contribution. Extracerebral veins have also been shown to affect fNIRS signals as a task-related systemic contribution.[34]

To deal with the above-described interference issues, various methods have been proposed.[10] The validity of these methods, however, was confirmed by making certain assumptions, namely (expected) waveforms,[35,36] contrast-to-noise ratio,[37] and correlation with laser-Doppler signals.[38,39] Few studies, however, have verified such methods by spatial analysis using simultaneous measurement by fNIRS and functional magnetic resonance imaging (fMRI). On the other hand, for providing higher spatial resolution, diffuse optical tomography using high-density probe arrangements has been proposed,[40,41] and this technique was found to be consistent with nonsimultaneous fMRI. Although general consistency between fNIRS and fMRI has been reported,[42–45] neither technique used multidistance optodes, and the purpose of these studies did not include the validation of methods for removing scalp effects. Through a concurrent multimodality study with fMRI and laser-Doppler flowmetry (LDF), a deep/shallow discrimination method can

*Address all correspondence to: Tsukasa Funane, E-mail: tsukasa.funane.sb@hitachi.com