Association between the Rostral Anterior Cingulate Cortex and Anterior Insula in the Salience Network on Response to Antidepressants in Major Depressive Disorder as Revealed by Isolated Effective Coherence

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Keywords
Rostral anterior cingulate cortex · Anterior insula · Antidepressants · Major depression · Isolated effective coherence

Abstract
Introduction: Functional connectivity is attracting increasing attention for understanding the pathophysiology of depression and predicting the therapeutic efficacy of antidepressants. In this study, we evaluated effective connectivity using isolated effective coherence (iCoh), an effective functional connectivity analysis method developed from low-resolution brain electromagnetic tomography (LORETA) and estimated its practical usefulness for predicting the reaction to antidepressants in theta and alpha band iCoh values.

Methods: We enrolled 25 participants from a depression treatment randomized study (the GUNDAM study) in which electroencephalography was performed before treatment. We conducted iCoh between the rostral anterior cingulate cortex (rACC) and anterior insula (AI), which are associated with the salience network. The patients were divided into responder and nonresponder groups at 4 weeks after the start of treatment, and iCoh values were compared between the two groups. Additionally, the sensitivity and specificity of iCoh were calculated using the receiver-operating characteristic (ROC) curve.

Results: The Mann-Whitney U test showed significantly weaker connectivity flow from the rACC to the left AI in the alpha band in the responder group. The ROC curve for the connectivity flow from the rACC to the left AI in the alpha band showed 82% sensitivity and 86% specificity.

Discussion/Conclusion: These findings suggest the pathological importance of effective connectivity flow from the rACC to the left AI in the alpha and theta bands and suggest its usefulness as a biomarker to distinguish responders to antidepressants.
Introduction

Pharmacotherapy with antidepressants is the standard protocol for treating patients with moderate to severe depression. However, initial monotherapy with antidepressants is ineffective in about 50% of patients [1]. No consensus has been reached on subsequent treatment strategies for patients with an inadequate response to initial treatment. Predicting treatment efficacy can reduce the mental and physical burden on patients during initial treatment. Therefore, the ability to predict the therapeutic effects of antidepressants in advance is considered to be of great significance. To this end, the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) study [2] and the International Study to Predict Optimized Treatment for Depression (iSPOT-D) [3] are attempting to establish biomarkers to predict treatment response to antidepressants.

Electroencephalography (EEG) is more convenient, economical, and less invasive than other neuroimaging techniques such as functional magnetic resonance imaging and positron emission tomography (PET). For several decades, quantitative EEG has been gaining attention as an objective measure of treatment response in patients with depression. In one of the earliest studies, Bruder et al. [4] focused on asymmetric alpha activity in resting EEG and reported that depressive patients with higher alpha activity in the right hemisphere showed poorer response to fluoxetine. Subsequently, studies were conducted to determine response rates to escitalopram using formulas based on theta and alpha activity at baseline and 1 week posttreatment [5]. More recently, a multicenter study was conducted with a larger number of participants using a machine learning algorithm [6]. However, conventional quantitative EEG analysis has had a difficulty in explaining the details of brain regions that have been suggested to be closely related to treatment response to antidepressants. To overcome this issue, Pascual-Marqui [7] developed low-resolution brain electromagnetic tomography (LORETA), an analysis method that greatly improves spatial resolution, which is a weakness of conventional EEG. eLORETA, described in detail in Pascual-Marqui [8, 9], was used for the localization of cortical electric activity. This is a distributed linear inverse solution to the EEG/MEG, which has the property, under ideal conditions, of zero localization error to all test point sources. This property is not shared by other linear methods, as shown in Pascual-Marqui et al. [10]. This capability can be used to assess functional brain connectivity based on high time resolution electrophysiology, which is not possible with other neuroimaging modalities [11–14].

The brain regions associated with the treatment response to antidepressants were initially focused on activity in the rostral anterior cingulate cortex (rACC), which was discovered by functional brain imaging studies other than EEG. Using PET, Mayberg et al. [15] reported that resting glucose metabolism levels in the rACC may predict the treatment response to antidepressants prior to the initiation of drug treatment. After their report, using LORETA, Pizzagalli et al. [16, 17] reported that theta activity in the rACC prior to treatment initiation could predict the treatment response to antidepressants. In addition, Pizzagalli et al. [16, 17] conducted another large randomized controlled trial in 248 patients from the EMBARC study to examine the relationship between antidepressant treatment response and activity in the theta band of the rACC. They reported that depressed patients with greater pretreatment theta band activity of the rACC showed better response to sertraline [18].

Recently, functional connectivity between brain regions that form large-scale brain networks, such as the default mode network (DMN), salience network (SN), and central executive network, has been the focus of much attention in gaining a better understanding of brain function in complex cognitive and emotional processing [19]. It is becoming clear that disruptions in these brain networks are closely related to psychiatric disorders such as schizophrenia, depression, bipolar disorder, and attention-deficit hyperactivity disorder [20]. Some studies have also examined functional connectivity in key brain regions of the brain networks described above and the response to antidepressant treatment for depression. Whitton et al. [21] showed that the antidepressant effect of sertraline on depression can be predicted from excess theta band functional connectivity in the rACC (the main hub of the DMN) and right anterior insula (AI) (the main hub of the SN) prior to treatment. Geuﬀes et al. [22] also reported similar results in the Netherlands Study of Depression and Anxiety (NESDA), where reduced right AI connectivity within the SN was associated with an inadequate treatment response to antidepressants.

Functional connectivity between brain regions has been identified using independent component analysis and synchrony analysis from neuroimaging tools such as EEG, MEG, blood oxygen level-dependent functional magnetic resonance imaging, and PET [23–25]. Functional connectivity is generally not a mechanism that directly indicates connectivity between brain regions. Ef-
effective connectivity, on the other hand, is defined as the coupling between causal regions and is generally identified using computational methods such as dynamic causal models, structural equation models, and Granger causality [26]. Interestingly, effective connectivity is distinctly different from functional connectivity. Friston [26] states that effective connectivity may be better suited to explain the connections between brain regions represented by functional connectivity in more detail.

Some methods have been developed to assess effective connectivity using EEG, among which, isolated effective coherence (iCoh) analysis, which uses LORETA to calculate effective connectivity between brain regions, is one of the more outstanding. iCoh analysis can determine whether the signal between regions flows from region A to region B or vice versa [27], whereas conventional effective coherence analysis methods such as partial directed coherence [28] can evaluate only the strength of the causal coherence between two regions. Recently, a few studies have applied this technique to show effective connectivity between the brain regions that affect treatment-resistant schizophrenia [29] and cognitive tasks [30].

Functional connectivity between the rACC and AI has received increasing attention for aiding understanding of the pathophysiology of depression and its potential as a clinical biomarker of the therapeutic efficacy of antidepressants [21, 22, 31, 32]. However, to the best of our knowledge, no reports have examined effective connectivity between the rACC and AI regions and the therapeutic effects of antidepressants using iCoh analysis.

We hypothesized, as in previous studies [21], that effective connectivity in the theta band between the rACC and AI would be associated with the response to antidepressant treatment. Our secondary hypothesis concerns iCoh in the alpha band between the rACC and AI because previous studies have reported that left-right neurophysiological characteristics appeared in not only the theta band but also the alpha band [33–35]. As an exploratory analysis, we measured the area under the curve (AUC) and calculated the sensitivity, specificity, and cutoff values of iCoh to predict the response to antidepressant treatment.

Specifically, we performed iCoh analysis of EEG data from pretreatment patients with depression to compare differences in effective connectivity between the rACC and left and right AI in responders and nonresponders at 4 weeks after the start of antidepressant treatment. In addition, we measured the (AUC and calculated the sensitivity, specificity, and cutoff iCoh values to identify significant differences in effective connectivity.

**Methods**

**Study Design**

We used EEG data obtained from patients with depression who participated in the Genotype Utility Needed for Depression Antidepressant Medication (GUNDAM) study, a randomized controlled study conducted in Japan to examine the therapeutic responses to and tolerability of antidepressants, and who consented to undergo EEG before treatment initiation [36]. All patients received one of the following oral antidepressants for 4 weeks (4 W): paroxetine, sertraline, or mirtazapine. Concomitant use of psychotropic drugs was forbidden, but the use of low-dose sleep-inducing drugs at bedtime was permitted. The primary clinical end point was score on the 17-item Hamilton Rating Scale for Depression (HAM-D17). In this study, we analyzed the scores at treatment week 0 (0 W), which was the time of study enrollment, and treatment week 4. The pretreatment EEG data obtained in the drug-free state were analyzed to evaluate the therapeutic response to antidepressants for each end point.

### Table 1. Demographic data

|                         | Responders (n = 14) | Nonresponders (n = 11) | p value |
|-------------------------|---------------------|------------------------|---------|
| Age, years (mean/SD)    | 54.29/17.84         | 49.91/16.84            | ns      |
| Sex (male/female)       | 6/8                 | 3/8                    | ns      |
| First episode, n (%)    | 7 (50)              | 4 (36)                 | ns      |
| Recurrent episodes, n (%)| 5 (36)              | 6 (55)                 | ns      |
| Smoking, n (%)          | 2 (14)              | 1 (9)                  | ns      |
| Drinking, n (%)         | 4 (29)              | 1 (9)                  | ns      |
| **Type of antidepressants** |                    |                        |         |
| SSRI, n (%)             | 7 (50)              | 6 (55)                 | ns      |
| NaSSA, n (%)            | 7 (50)              | 5 (45)                 | ns      |
| HRSD-17 total score 0 W (mean/SD) | 19.21/4.31 | 21.00/2.49            | ns      |

SSRI, selective serotonin reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; HRSD-17, Hamilton Rating Scale for Depression-17.
Table 2. Coordinates of regions of interest used for isolated effective coherence (MNI coordinates in mm)

| Region  | x    | y    | z    |
|---------|------|------|------|
| rACC    | 0    | 45   | 0    |
| l-AI    | −30  | 24   | −13.5|
| r-AI    | 30   | 24   | −13.5|

MNI, Montreal Neurological Institute; rACC, rostral anterior cingulate cortex; l-AI, left anterior insula; r-AI, right anterior insula.

Table 3. Results of the Mann-Whitney U test for differences in iCoh values connected the rACC and AI in the theta band

| iCoh → | U    | Z    | r    | p  value |
|---------|------|------|------|---------|
| HAM-D scores for responders versus nonresponders |
| Theta   |
| rACC    | r-AI | 121  | 2.409| 0.048   | 0.015 |
| rACC    | l-AI | 91   | 0.766| 0.15    | 0.467 |
| l-AI    | rACC | 52   | −1.369| −0.27   | 0.183 |
| r-AI    | rACC | 105  | 1.533| 0.31    | 0.134 |

rACC, rostral anterior cingulate cortex; l-AI, left anterior insula; r-AI, right anterior insula (p < 0.0125; Bonferroni correction).

Table 4. Results of the Mann-Whitney U test for differences in iCoh values connected the rACC and AI in the alpha band

| iCoh → | U    | Z    | r    | p  value |
|---------|------|------|------|---------|
| HAM-D scores for responders versus nonresponders |
| Alpha   |
| rACC    | r-AI | 125  | 2.628| 0.53    | 0.008* |
| rACC    | l-AI | 108  | 1.697| 0.34    | 0.095 |
| l-AI    | rACC | 52   | −1.369| −0.27   | 0.183 |
| r-AI    | rACC | 108  | 1.697| 0.34    | 0.095 |

rACC, rostral anterior cingulate cortex; l-AI, left anterior insula; r-AI, right anterior insula. * p < 0.0125; Bonferroni correction.

Participants

Of the patients with depression who participated in the GUN-DAM study, 25 who consented to undergo EEG were included in the present study (Table 1). Depression was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). All participants were recruited from the outpatient clinic of the Department of Neuropsychiatry, Kansai Medical University Medical Center.

EEG Recordings

All participants underwent EEG once at least 2 weeks before starting treatment with antidepressants. EEG was performed using an EEG-1100 electroencephalograph (Nihon Kohden, Tokyo, Japan). EEG electrodes were placed on 19 locations on the scalp (Fp1/2, F3/4, C3/4, P3/4, O1/2, F7/8, T3/4, T5/6, Pz, Cz, and Pz) according to the international 10/20 system, and the reference electrodes were placed on both earlobes. EEG was performed for approximately 20 min with the eyes closed at rest. A bandpass filter was applied in the range of 0.3–30 Hz.

Effective Connectivity Analysis

We used LORETA-KEY software (http://www.uzh.ch/keyinst/loreta.htm) [37] for the iCoh analysis. For each participant, the EEG data obtained after 3 min of EEG recording were extracted by excluding the effects of a small number of visually detectable artifacts such as body and eye movements. We then used the artifact detection algorithm in LORETA-KEY to reduce the number of artifact-affected epochs. As a result, a total of 60 s (2 s × 30 epochs) of data were adapted.

For the coordinates of the rACC and AI, a pair of regions of interest for effective connectivity, we referred to previously described data [38] (Table 2). The frequency bands used in the analysis were the theta band (4–8 Hz), alpha band (8.5–13 Hz), and supplementary beta bands (beta 1: 13.5–20 Hz and beta 2: 20.5–30 Hz).

Statistical Analyses

For the main analysis, we defined a responder as a patient with 50% or greater improvement in the HAM-D score at 4 weeks compared with the score at 0 weeks. IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA) was used for the analysis.

First, we performed the Shapiro-Wilk test for normality. We conducted the Mann-Whitney U test to compare the iCoh values connecting the rACC and AI in the theta band between the responders and nonresponders. Multiple comparisons, because there are four iCoh variables in the theta band, we used the Bonferroni correction and an adjusted significance level of p < 0.0125 (= 0.05/4). Second, we performed the same test for the iCoh values connecting the rACC and AI in the alpha band between the responders and nonresponders. Supplementary beta band was analyzed in the same way.

Third, we conducted receiver-operating characteristic (ROC) curve analysis and calculated the AUC for the iCoh variables that showed significant differences in the previous analyses. Next, we conducted ROC curve analysis and calculated the AUC for the iCoh variables that showed significant differences in the previous analyses.

Finally, we performed multiple regression analysis with sex, age, baseline HAM-D score, smoking, and alcohol consumption as independent variables to ascertain the factors affecting the iCoh values of the rACC and AI at baseline. The iCoh values between the rACC and AI used as dependent variables were transformed to natural logarithms. The level of significance was set at p < 0.05.

Results

Demographic Characteristics

The participants’ demographic characteristics are shown in Table 1. There were 14 responders and 11 nonresponders, and no significant differences were found be-
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tween characteristics such as sex, first episode, recurrent episodes, smoking, drinking, prescribed antidepressants, or baseline HAM-D score (0 W). There were no dropouts among the 25 patients who participated in the study. Differences in demographic characteristics between the responders and nonresponders were calculated using the t test or χ² test.

Comparison of iCoh Values Connecting the rACC and AI in the Theta Band between Responders and Nonresponders

The results of the Mann-Whitney U test for differences in iCoh values connecting the rACC and AI in the theta band between the responders and nonresponders are shown in Table 3. No significant differences were found in the theta band, but marginally (U = 121.0; p = 0.015).

Comparison of iCoh Values Connecting the rACC and AI in the Alpha Band between Responders and Nonresponders

The results of the Mann-Whitney U test for differences in iCoh values connecting the rACC and AI in the alpha band between the responders and nonresponders are shown in Table 4. The findings revealed that the connectivity flow value from the rACC to the left AI in the alpha band was significantly smaller in responders than in nonresponders (U = 125.0; p = 0.008) (Fig. 1). The effect size using z-scores was r = 0.53, indicating a large difference.

Comparison of iCoh Values Connecting the rACC and AI in the Beta Bands between Responders and Nonresponders

The results of the Mann-Whitney U test for differences in iCoh values connecting the rACC and AI in the beta bands between the responders and nonresponders are shown in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000525338). No significant differences were found in the beta bands, but marginally (beta 1: U = 122.0; p = 0.013, beta 2: U = 117.0; p = 0.029).

ROC Curve Analysis of iCoh Values from the rACC to Left AI in the Theta Band in Responders and Nonresponders

The ROC curves of the iCoh values from the rACC to the left AI in the theta band for responders and nonresponders are shown in Figure 2. The AUC was 0.786, the optimal cutoff value based on Youden’s index was 0.008, and the sensitivity and specificity were 91% and 64%, respectively.

ROC Curve Analysis of iCoh Values from the rACC to Left AI in the Alpha Band in Responders and Nonresponders

The ROC curves of the iCoh values from the rACC to the left AI in the alpha band for responders and nonresponders are shown in Figure 3. The AUC was 0.812, the optimal cutoff value based on Youden’s index was 0.03,
and the sensitivity and specificity were 82% and 86%, respectively.

**Influencing Factors on iCoh Values**

Multiple regression analysis showed that factors such as gender, age, alcohol consumption, smoking, and baseline HAM-D score (0 W) were not significantly different in terms of iCoh values from the rACC to left AI across all bands.

**Discussion/Conclusion**

Our study suggested that weak effective connectivity from the rACC to left AI, not only theta band but also alpha band to be more important. These may be an indicator to distinguish between responders and nonresponders in depressive patients before treatment with antidepressants. To the best of our knowledge, this is the first study to report that the therapeutic response to antidepressants can be
predicted from pretreatment effective connectivity between the rACC and AI based on iCoh analysis. Additionally, the AUC showed high sensitivity and specificity for detecting responders and nonresponders using iCoh values for the rACC to left AI.

The rACC is generally involved in processing emotions [39]. Through its connection with other brain regions, it also plays a central role in signal processing (e.g., top-down and bottom-up transmission of stimuli) and appropriate control of other brain regions [40]. To control other brain regions, the rACC functionally synchronizes with the AI and forms the SN, which is involved in switching between externally and internally oriented cognition through the DMN and central executive network [41, 42]. The relationship between these networks and EEG has been attracting increasing attention [43]. In addition, a recent paper reported that the effects of drug therapy with antidepressants can be predicted from functional connectivity in resting state networks [44]. Our results support these findings through the confirmation of the importance of signal transmission through the rACC in depression.

Regarding the association with depression, the SN has been identified as one of the most important regions associated with the therapeutic effects of antidepressants [21, 22]. It is reported to be associated particularly with functional connectivity between the rACC and right AI. Another paper using PET also reported that the right AI is important in terms of prediction in selecting treatments for depression [45]. Although the AI is particularly important in terms of connectivity, our results revealed effective connectivity between the left AI and rACC, suggesting that not only the right AI but also the left AI may be important in depression.

According to the present results, contrary to our hypothesis, only a marginal difference was seen in the theta band, which could be caused by the region of interest in the brain. Previous studies on the response to antidepressant treatment mainly focused on theta band activity in the rACC [16–18, 46, 47]. On the other hand, some studies on the antidepressant effect in the alpha band have reported differences in left-right hemisphere activity [4, 48]. The present results regarding alpha band activity showed significantly weak connectivity flow from the rACC to the left AI in the alpha band, which supports previous studies that reported left-right hemispheric differences in the alpha band.

The sensitivity and specificity in the present study were high, even though we used only one EEG point in the pretreatment period. A previous paper adapted the Antidepressant Treatment Response (ATR) index for predicting the response to selective serotonin reuptake inhibitors [5]. In that paper, the ATR index, which is calculated from theta and alpha EEGs of the forehead twice before and at 1 week after treatment, showed 58% sensitivity and 91% specificity. In the present study, the sensitivity was 82% and the specificity was 86% in the alpha band, similar to the results of the ATR index. However, despite the fact that ATR requires two EEG measurements, our results required only baseline measurements, which are more practical for clinical application from the viewpoint of patient burden.

Although a recent meta-analysis [49] reported that quantitative EEG was less useful, many points still need to be considered in regard to the methods and conditions of analysis. For example, sleep EEG has been reported to be useful for diagnosing depression [50]. In recent years, there have also been promising studies using machine learning [51]. Furthermore, as demonstrated by our results, EEG, with its superior temporal resolution, has allowed new discoveries by incorporating information between brain regions revealed by brain functional imaging. Therefore, the combination of depression and EEG may be a promising field for future research.

This study has several limitations. First, the type and dosage of antidepressants used and the small amount of concomitant sleep-inducing drugs were not standardized. Each participant was treated with one antidepressant for the same duration, and the doses were adjusted in the same manner. Kato et al. [36] reported that the treatment effects did not differ between antidepressants after 4 weeks of treatment. However, for an improved study design, a comparison with uniform antidepressant uses or placebo medication is needed.

Second, we did not assess effective connectivity after 4 weeks of antidepressant treatment. A comparison of changes in effective connectivity before and after treatment would allow for a more detailed examination of the relationship between antidepressants and treatment efficacy.

Third, this study had a relatively small sample size; however, it was conducted as a randomized controlled trial and showed statistically significant results. Further validation by means of larger-scale studies with more participants, more frequent EEGs, and more detailed analyses of EEG data is needed.

The results of the present study indicate that weak iCoh from the rACC to the left AI may be a biomarker to distinguish responders to antidepressants from nonresponders. iCoh analysis is a useful method for analyzing effective connectivity that directly indicates connections between regions of interest. Therefore, iCoh analysis may lead to a
better understanding of connectivity between regions of interest to predict the response to antidepressants.

Statement of Ethics

This study was approved by Kansai Medical University Ethics Committee (approval no. Hi 0910) and registered in the UMIN Clinical Trials Registry (UMIN000008451). Written informed consent was obtained from the participants.

Conflict of Interest Statement

The authors have had the following interests for the past 3 years. S.M. has received speaker’s honoraria from Meiji-Seika Pharma. M.K. has received grant funding from the Japan Society for the Promotion of Science, the Ministry of Health, Labour and Welfare of Japan, the Japan Agency for Medical Research and Development, the SENSIN Medical Research Foundation, and Japan Research Foundation for Clinical Pharmacology, and speaker’s honoraria from Sumitomo Dainippon Pharma, Otsuka, Meiji-Seika Pharma, Eli Lilly, MSD K.K., GlaxoSmithKline, Pfizer, Janssen Pharmaceutical, Shionogi, Mitsubishi, Tanabe Pharma, Takeda Pharmaceutical, Lundbeck, and Ono Pharmaceutical. S.I. has received young research grant funding from the Smoking Research Foundation and speaker’s honoraria from Sumitomo Dainippon Pharma, Otsuka, Meiji-Seika Pharma, Eli Lilly, MSD K.K., Pfizer, Janssen Pharmaceutical, Takeda Pharmaceutical, and Lundbeck. M.Y. has received grant funding from the Japan Society for the Promotion of Science and speaker’s honoraria from Eisai, Daiichi-Sankyo, MSD K.K., Ono Pharmaceutical, and Viatris. Y.T. has received grant funding from the Japan Society for the Promotion of Science and speaker’s honoraria from Eisai, MSD K.K., Daiichi-Sankyo, Pfizer, UCB Japan, Novartis, and Ono Pharmaceutical. T.K. has received speaker’s honoraria from Otsuka, Dainippon-Sumitomo Pharma, Meiji-Seika Pharma, Janssen Pharmaceutical, Eisai, Daiichi-Sankyo, Takeda Pharmaceutical, Lundbeck, and Ono Pharmaceutical. K.N. has received speaker’s honoraria from Dainippon-Sumitomo Pharma and Meiji-Seika Pharma. Y.K. and S.U. declare no conflicts of interest associated with this manuscript.

Funding Sources

This study was supported by a Grant-in-Aid for Scientific Research (23591684) and a Grant-in-Aid for Early-Career Scientists (18K15499) from JSPS KAKENHI, and by the Centre of Innovation Programme of the Japan Science and Technology Agency (JP-MJCE1310). These agencies had no roles in the preparation of the data or manuscript.

Author Contributions

Masaki Kato designed the study. Masaki Kato, Masafumi Yoshimura, Yosuke Koshikawa, Toshiteru Takekita, Toshihiko Kinoshita, and Keiichiro Nishida contributed to the acquisition of data. Shota Minami, Shunichiro Ikeda, Masafumi Yoshimura, Satoshi Ueda, Toshihiko Kinoshita, and Keiichiro Nishida conducted the analyses. Shota Minami, Masaki Kato, and Keiichiro Nishida wrote the first draft of the manuscript. Shota Minami, Masaki Kato, Shunichiro Ikeda, Masafumi Yoshimura, Satoshi Ueda, Yosuke Koshikawa, Toshiteru Takekita, Toshihiko Kinoshita, and Keiichiro Nishida revised and approved the final version.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further enquiries can be directed to the corresponding author.

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Neuropsychobiology 2022;81:475–483
DOI 10.1159/000525338

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