B. 研究方法

3次元脳構造画像とrs-fMRIのプロトコルを持ち寄って、議論を重ねて、共通プロトコルの作成を行った。臨床指標についても、プロトコルを持ち寄って、議論を重ね共通指標を作成した。共通プロトコールに基づいてMRIデータ（T1強調画像、resting-state fMRI、拡散テンソル画像）の収集を行う。

C. 研究結果

研究班会議において、本研究の基盤となる共通撮像プロトコールを決定し、臨床評価項目を確定した。神奈川県立精神医療センターならびに昭和大学附属烏山病院での気分障害患者ならびに健常者の被験者リクルート体制を構築した。平成26年6月には、神奈川県立精神医療センターの倫理審査委員会での審議を受け承認を受けた。更に平成26年7月には、昭和大学附属烏山病院において倫理審査委員会の審議を受けて承認を受けた。

サンプル収集の中軸となるのが、昭和大学附属烏山病院に新規に導入された3テスラMRI装置である。平成26年10月より、健常者のMRIデータの取得を開始して、平成26年度内で計16名の健常被験者のMRIデータを取得した。平成27年度は患者データを中心に取得する予定である。また、神奈川県立精神医療センターで行っているrTMS（反復性経頭蓋磁気刺激法）の臨床試験において、rTMS前後の縦断的なMRIデータの集積も行う予定である。

D. 考察

今まで、精神医学研究においては、各施設での検査方法や臨床評価方法が異なるため、大規模な多施設共同研究は難しかった。よって、今回、本邦の脳画像研究の中核的な研究機関が集まって、方法論の統一を行ったことは、画期的であると言える。今後、共通化した方法論を用いた成果が得られることにより、実用化に近づくことができると考えられる。

E. 結論

我々は、共通化したMRIプロトコルと臨床指標の作成を行った。残り1年間（平成27年度）継続して研究を行うことによって得られると考えられる診断補助法は、医療行政上、大変有意義であり、国民の保健・精神医療において多大なる貢献ができると考えられる。

F. 研究発表

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G. 知的財産権の出願・登録状況（予定を含む）

1.　特許取得

該当なし。

2.　実用新案登録該当なし。

3.　その他

該当なし。

Ⅲ.　業績一覧

平成２６年度厚生科学研究費補助金（難病・がん等の疾患分野の医療の実用化研究事業）
分担研究報告書

MRIを用いた気分障害の診断補助法についての実用化研究
分担研究課題：構造MRIプロトコル作成、品質管理、診断アルゴリズム作成、診断ソフトウェア開発

研究分担者　山下　典生
岩手医科大学医歯薬総合研究所超高磁場MRI診断・病態研究部門 助教

研究要旨

本分担研究ではMRIを用いた気分障害の診断補助法を開発するため、構造MRI画像の撮像プロトコル作成、画像品質管理、診断アルゴリズムの作成および診断ソフトウェア開発などを行っている。本年度は昨年度策定した共通プロトコルを用いて撮像したテストデータの画質評価を行った。また、以前から議論の対象となっている1mm等方ボクセルでの撮像が標準プロトコルのスライス厚1.2mmでの撮像と異なる解析結果を生じるかについて、ボランティア、統合失調症患者のデータを用いて比較解析を行った。さらにこれら画質の評価に加え、脳体積解析の精度向上のため、ファントムを用いた幾何歪みの補正プログラムを開発して班員内で共有した。

A. 研究目的

本研究では気分障害の診断補助法の開発の一環として、構造MRI画像の撮像プロトコルの標準化、原画像および解析結果の品質管理法や高精度脳体積計測法、診断アルゴリズムなどを開発し、最終的にこれらをまとめて診断ソフトウェアとしてパッケージ化することで気分障害の診断補助法を実用化することを研究の目的としている。

本年度は昨年度策定したプロトコルによって撮像されたテストデータの画質評価や画像付帯情報による撮像条件の確認等を行い、一貫した撮像プロトコルによる安定した高品質な画像データの取得を目指した。また、かねてより議論の対象となっている、1mm等方ボクセルで撮像した画像の品質が標準プロトコルのスライス厚1.2mmで撮像した画像と異なるかについて、ボランティアおよび統合失調症患者のデータを用いて比較検討を行った。さらに、画質のデータ脳体積解析の精度向上のため、得られた画像データに対して後処理によって幾何歪みの補正を行うソフトウェアを開発し、班員内で共有した。

B. 研究方法

画像データの品質管理について、昨年度策定したプロトコルによってファントムやボランティアのテスト撮像を行い、取得したデータの画質評価、および画像付帯情報のチェックを専用のビューワやプログラムで行った。

1mm等方ボクセル（画素サイズ1.0×1.0×1.0mm）とスライス厚1.2mm（画素サイズ1.0×1.0×1.2mm）の撮像条件の差の検討では、両撮像条件でデータを収集した健常者19例、統合失調症患者20例のデータを用いてVoxel-based morphometryと自動ROI解析を行い、解析手法ごとに撮像条件間での差を対応のあるｔ検定で比較検討した。

ファントムを用いた幾何歪み補正プログラムは米国Alzheimer's Disease Neuroimaging Initiative（ADNI）で開発されたADNIファントムの解析プログラムを利用して新規に開発した。プログラムの内容は、まずファントム解析プログラムによって推定された歪み情報を取得し、この歪みを補正する画像変形のパラメータを計算・保存する。次に別の検査で取得したデータに対してこの画像変形を施す事で歪みを補正した画像を生成する。画像変形には多項式近似を用いて、先行報告（舞草ら、Med Phys 2013）で示されたBayesian情報基準量によって最適なx,y,z各軸方向の変形の多項式近似の次数を自動で選択できる仕様とした。

C. 研究結果

画像データの品質管理について、各施設で収集されたデータをDICOMビューワで確認し、画質に問題

のないことを確認した。撮像プロトコルの遵守については、規定の撮像マトリクス数からの変更などが見つかり、施設に問い合わせの上修正を行なった。

1mm 等方ボクセル撮像の影響について、VBM を用いた結果では扁桃体、海馬、海馬傍回、中心後回、帯状回などで撮像プロトコル間の差を検出した。これは自動 ROI 体積によってさらに詳細に検討されたが効果量は小さく、全脳の関心領域 136 部位中、8 割以上の部位（健常者 118、疾患群 113 部位）で 1%未満の体積変動しかないことが明らかとなった。ただし、扁桃体では 5%の体積変動を示すなど部位特異的な所見も明らかとなった。

歪み補正のプログラムは汎用脳画像解析ソフトウェアパッケージである SPM バージョン 8 をベースに、研究者が簡便に利用できるようにユーザインターフェースを開発して SPM のツールボックスとして実装した。歪み補正の効果は、ファントム画像を用いて歪み補正前後で歪み計測を行ない、補正後に歪みの大きさが明らかに減少していることによって検証した。ボランティアのデータに対しても定性的に（視認で）歪み補正の効果を確認したが、、今後定量的な検討を行う予定である。

D. 考察

昨年度策定した撮像プロトコルでのデータ収集が順調に進み、現在は継続的な画像データの品質管理を行っている段階である。本研究班では既にファントムによる MR 装置のモニタリング、自動画像分離抽出アルゴリズムを利用した被験者データからの画像品質管理指標の抽出手法などを確立しているため、長期間に渡る安定したデータ収集が可能となっている。また、単一装置での結果ではあるものの、これまで不明であった 1mm 等方ボクセル撮像の標準プロトコル（スライス厚 1.2mm）に対する影響が明らかとなり、施設の選択によって 1mm 等方ボクセルを選択している場合においても体積値に与える影響は概して少ないことが分かった。ただし、扁桃体など深部灰白質などで～5%程度の体積変動を示しており、部位によっては解析時に特別な注意を払う必要がある可能性を示唆した。

脳体積測定の精度向上のため作成した、ファントム画像を利用した歪み補正プログラムではその効果がファントム解析によって確かめられ、また汎用脳画像解析ソフトウェアのツールボックスとして実装したことで今後研究者が利用しやすい環境を整えた。

E. 結論

継続的な画像データの品質管理体制を確立し、またスライス厚の異なる撮像プロトコル間での体積変動の大きさを明らかにした。さらに、新規に脳体積測定の精度向上のための歪み補正プログラムを開発し、構造 MRI を用いた気分障害の診断補助法開発の基盤を整えたと言える。次年度以降、収集されたデータの詳細な解析を行い、気分障害を鑑別する定量的な解析指標の開発を行う予定である。

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2. 学会発表

なし

G. 知的財産権の出願・登録状況（予定を含む）

1. 特許取得

出願番号：特願 2014-239811
発明者：山下　典生、後藤　俊介
発明の名称：磁気共鳴イメージング装置用ファントム
出願人：学法人岩手医科大学、有限会社ライトム
出願日：2014/11/27

2. 実用新案登録

該当なし

3. その他

該当なし

研究成果の刊行に関する一覧表

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著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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Ohi K, Hashimoto R, Ikeda M, Yamashita F, Fukunaga M, Nemoto K, Ohnishi T, Yamamori H, Yasuda Y, Fujimoto M, Umeda-Yano S, Watanabe Y, Iwata N, Weinberger DR, Takeda M.	Genetic risk variants of schizophrenia associated with left superior temporal gyrus volume	Cortex	58C	23-26	2014
Watanabe Y, Tanaka H, Tsukabe A, Kunitomi Y, Nishizawa M, Hashimoto R, Yamamori H, Fujimoto M, Fukunaga M, Tomiyama N.	Neuromelanin magnetic resonance imaging reveals increased dopaminergic neuron activity in the substantia nigra of patients with schizophrenia	PLos One	11:9(8)	e104619	2014

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Fujihara K, Narita K, Suzuki Y, Takei Y, Suda M, Tagawa M, Ujita K, Sakai Y, Narumoto J, Near J, Fukuda M	Relationship of γ-aminobutyric acid and glutamate + glutamine concentrations in the perigenual anterior cingulate cortex with performance of Cambridge gambling task	NeuroImage	印刷中	印刷中	印刷中
細田千尋、花川 隆	言語能力の向上・減退と脳可塑性の検討 ー多次元イメージング法を用いた脳可塑性の可視化ー	精神科	25(2)	192-195	2014
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Yoshino M, Kin T, Ito A, Saito T, Nakagawa D, Kamada K, Mori H, Kunimatsu A, Nakatomi H, Oyama H, Saito N.	Diffusion tensor tractography of normalfacial and vestibulocochlear nerves	J Comput Assist Radiol Surg	10	383-392	2015

Ⅳ.　研究成果の刊行物・別刷

BIPOLAR DISORDERS
AN INTERNATIONAL JOURNAL OF PSYCHIATRY AND NEUROSCIENCES

Bipolar Disorders 2014

BIPOLAR DISORDERS

Original Article

Dorsolateral prefrontal hemodynamic responses during a verbal fluency task in hypomanic bipolar disorder

Nishimura Y, Takahashi K, Ohtani T, Ikeda-Sugita R, Kasai K, Okazaki Y. Dorsolateral prefrontal hemodynamic responses during a verbal fluency task in hypomanic bipolar disorder.
Bipolar Disord 2014: 00: 000–000. © 2014 John Wiley & Sons A/S.
Published by John Wiley & Sons Ltd.

Objectives: Neuroimaging studies have suggested prefrontal dysfunction in response to cognitive activation in bipolar disorder (BD). However, its characteristics in manic states have not been well understood. Thus, we compared prefrontal hemodynamic responses during a cognitive task between hypomanic and depressive states in BD. We then longitudinally compared hypomanic and subsequent euthymic states.

Methods: The prefrontal function of 27 patients with BD (11 hypomanic and 16 depressed) and 12 age- and gender-matched healthy controls (HCs) was evaluated using near-infrared spectroscopy (NIRS) during a verbal fluency task (VFT). Hypomanic symptoms were assessed using the Young Mania Rating Scale. Among the 11 hypomanic patients, eight participated in the second NIRS measurement after their hypomanic symptoms resolved.

Results: VFT performance did not differ among hypomanic, depressed, and HC groups. Both BD groups exhibited significantly lower activation during the VFT than HCs in the broader bilateral prefrontal cortex. Hemodynamic changes in the left dorsolateral prefrontal cortex (DLPFC) in the hypomanic patients with BD were significantly larger than those in the depressed patients. In addition, hypomanic symptom severity was positively correlated with activation in the left DLPFC and frontopolar cortex in patients with BD. Follow-up measurement of the hypomanic patients revealed that prefrontal activation was decreased after hypomanic symptoms resolved.

Conclusions: Combining cross-sectional and longitudinal assessments, the present results suggest that prefrontal hemodynamic responses associated with cognitive activation differ between hypomanic and depressive states in BD. NIRS measurement could be a useful tool for objectively evaluating state-dependent characteristics of prefrontal hemodynamics in BD.

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doi: 10.1111/bdi.12252

Key words: bipolar disorder – executive function – hypomanic symptoms – near-infrared spectroscopy (NIRS) – prefrontal cortex

Received 12 October 2013, revised and accepted for publication 15 April 2014

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State-dependent changes in brain hemodynamic response are not well understood in bipolar disorder (BD). Converging evidence suggests the presence of neurocognitive dysfunction in individuals with BD (1). Among various cognitive functions, impairments in executive functioning have been reported across mood states (2), with some potential for improvement with treatment (3). Executive dysfunction in BD is associated with overall psychosocial functioning (4), occupational adaptation and poor interpersonal function (5–9), higher readmission rate (10),

and delayed recovery after acute-phase treatment (6).

In a number of functional neuroimaging studies on BD, one of the most consistent findings is abnormal limbic activation, including in the amygdala. Previous studies also indicate that prefrontal dysfunction affects the regulation of emotional and cognitive processing (11). Among the prefrontal subregions, the lateral prefrontal cortex (PFC) is a key structure for performing executive functions. Inconsistent results were obtained with regard to lateral prefrontal activity during an executive task associated with mood states in BD. Decreased activation in the ventrolateral PFC (VLPFC) across mood states in BD during an executive task was reported relatively frequently in past studies (11–13). Other studies indicated the hyperactivation of the dorsolateral PFC (DLPFC) and inferior frontal gyrus during euthymia in a verbal fluency task (VFT) (14, 15). However, few studies have performed a direct comparison in multiple mood states or obtained longitudinal follow-up measurements of prefrontal function in patients with BD, most often due to difficulties in immobilizing participants in a manic state during brain scanning.

Near-infrared spectroscopy (NIRS) is a non-invasive neuroimaging technique based on the principle of the absorption of near-infrared light into brain tissue. Taking advantage of the less-constrained measurement within a relatively short time, neuroimaging studies using NIRS devices have been performed with a variety of participants including infants (16, 17) and individuals with psychiatric disorders with variable illness severity and level of functioning (18–20). Non-invasive NIRS imaging allows for repeated measurements; intra-subject reproducibility has been confirmed on a monthly and yearly basis in healthy adults (21–23).

Previous NIRS imaging studies examining prefrontal functioning during an executive functioning task in patients with BD have shown inconsistent results. Most studies have reported hypofrontality in verbal fluency or working memory tasks (24–28), hyperfrontality in VFT (29), or differential time course of activation in VFT (30) in patients with BD compared to healthy controls (HCs). In addition, most participants in these NIRS studies were patients with depressed or euthymic mood (24–31) or patients with various mood states (29). Further, previous NIRS studies have not specifically compared patients based on their mood state.

We hypothesized that both hypomanic and depressed patients with BD would show decreased activation in the VLPFC compared to HCs, as previous reports have shown the dysfunction across mood states (3, 11, 24–28). Moreover, we hypothesized that left DLPFC activation would be observed only in depressed patients with BD due to the decreased left DLPFC activity associated with depression (32). Furthermore, we also hypothesized that PFC activation would decrease when participants' hypomanic symptoms resolved, as previous studies of mania have reported heightened (33) and state-dependent (34) activation in the amygdala as well as synchronization with DLPFC activity (35).

Thus, in the present study, we measured prefrontal function during an executive functioning task in hypomanic patients with BD. We used patients with BD in a depressive state as a comparison group in addition to healthy volunteers to examine whether executive function impairment was dependent on mood state. Moreover, we used NIRS to examine the correlation between prefrontal functioning and hypomanic symptom severity as assessed by the Young Mania Rating Scale. Furthermore, we conducted a follow-up measurement with the hypomanic patients after their manic symptoms resolved to evaluate whether the findings of the cross-sectional assessment could be replicated within the same individual.

Methods

Participants

Participants included 27 patients with BD [nine with bipolar I disorder (BD-I), 10 with bipolar II disorder (BD-II), and eight with BD not otherwise specified] according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (36) (DSM-IV-TR) and 12 HC participants. We matched participants in the HC and BD groups based on mean age and gender ($p > 0.05$). Participant exclusion criteria were as follows: left-handedness, a history of major physical illness, a neurological disorder, substance dependence, and a history of loss of consciousness due to head injury. In addition, the healthy subjects who had a history of neuropsychiatric disorder, assessed by the Mini-International Neuropsychiatric Interview (37), were excluded from this study. We also excluded participants having a first-degree relative(s) with psychiatric disorders in the HC group. Participants' premorbid IQ was estimated using the Japanese version of the National Adult Reading Test (JART) (38). All patients were taking medication at the time of NIRS measurement: lithium [hypomanic (n = 7), depressed (n = 6)], anticonvulsants [hypomanic (n = 7), depressed (n = 7)], antidepressants [hypomanic (n = 2), depressed (n = 10)], benzodiazepine

[hypomanic (n = 10), depressed (n = 14)], and/or antipsychotics [hypomanic (n = 9), depressed (n = 8)].

All subjects provided written informed consent, and the study protocols were approved by the Research Ethical Committee of the Tokyo Metropolitan Matsuzawa Hospital. This study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki of 1975.

Study design

In the hypomanic subgroup, we performed a cross-sectional assessment and subsequent longitudinal assessment. Of the 11 hypomanic patients who participated in the cross-sectional assessment, eight patients (seven male and one female) participated in the second NIRS measurement after their hypomanic symptoms resolved. The entry criterion for subsequent longitudinal assessment was at least 50% improvement in mania symptom severity as measured by the YMRS, compared to the first NIRS measurement. The three individuals who did not participate in the longitudinal assessment [mean age = 54.5 years, standard deviation (SD) = 8.4 years] were significantly older than these eight participants (mean age = 38.0 years, SD = 10.8 years, Mann–Whitney's *U*-test, p = 0.042). Analysis of other demographic variables did not show significant differences between these groups.

Clinical assessments

We used the Japanese versions of the Hamilton Rating Scale for Depression (HAM-D), 17-item version (39), and the Young Mania Rating Scale (YMRS) (40) to assess affective symptom characteristics and severity scores. BD phase was assessed by a trained psychiatrist (KT, TO, or RI). The YMRS score was used for assigning the participants with BD into depressed (n = 16) and hypomanic (n = 11) patient groups. The cutoff point for the YMRS was 4 (41). Participants' level of functioning was clinically characterized using the Global Assessment of Functioning [(GAF), DSM-IV-TR].

Cognitive task

A single-block design model of the VFT was employed to assess prefrontal activation. Participants were asked to remain seated, keep their eyes open, and avoid making any movements. The total measurement period was 160 sec, which consisted of a 30-sec pre-task period, a 60-sec task period, and a 70-sec post-task period (42–45). Participants were instructed to repeat a train of syllables during the pre- and post-task periods as follows: '/a/, /i/, /u/, /e/, /o/.' During the 60-sec task period, participants were instructed to generate as many words as possible, while the initial syllables were changed every 20 sec. Performance score was determined by the number of correct words generated by a participant.

NIRS measurement

Relative concentration changes of oxygenated (oxy-Hb) and deoxygenated (deoxy-Hb) hemoglobin (Hb) during the VFT were measured using a 52-channel NIRS machine (ETG-4000; Hitachi Medical Corporation, Tokyo, Japan). The machine uses two wavelengths of near-infrared light (695 and 830 nm) and calculates the amount of absorbed near-infrared light based on the modified Beer–Lambert law (46, 47). The distance between pairs of emitter and detector probes was 3.0 cm. The NIRS probes were placed on the participant's frontal region. The lowest probes were positioned along the T4-Fpz-T3 line according to the International 10/20 system. The probe arrangements could measure Hb from the bilateral prefrontal cortical areas [e.g., dorsolateral PFC (DLPFC) and ventrolateral PFC (VLPFC)], frontopolar cortex (FPC), and the anterior part of the temporal cortex (aTC), supported by anatomical cranio-cerebral correction via the International 10/20 system (48). The estimated cortical regions were localized at each channel by a virtual registration of NIRS (49–51).

The time resolution of the NIRS signal was 0.1 sec. A moving average window of 5 sec was adopted to remove any short-term motion artifacts. Further, we applied the automated method for artifact rejection focused on three types of noise (high frequency, low frequency, and no signal) and body-movement artifacts (44). Because we excluded the rejected channels from further analysis, the number of participants analyzed varied across channels (cross-sectional assessment) as follows: HC (the range of the number of participants analyzed in 52 channels): 8–12 (mean = 11.4, 95.2%); BD depressed patients: 12–16 (mean = 15.5, 96.9%); and BD hypomanic patients: 9–11 (mean = 10.6, 96.5%). Longitudinal assessment was as follows: BD hypomanic (+): 5–8 (mean = 7.2, 90.0%); BD hypomanic (−): 6–8 (mean = 7.6, 94.7%).

To examine task-related activation, data were analyzed using the *Integral Mode* loading with the ETG-4000 machine, in which the pre-task baseline

is determined as the mean over a 10-sec period just prior to the task period, and the post-task baseline is determined as the mean over the last 10 sec of a 70-sec post-task period. Linear fitting was performed using the data obtained between the two baselines. After the artifact rejection, grand mean waveforms averaged across subjects were calculated in each channel and in each group to observe the whole activation pattern throughout the VFT.

Statistical analysis

All statistical analyses were performed using PASW Statistics 18.0 (SPSS Japan Inc., Tokyo, Japan). For statistical analysis, we calculated the average changes in oxy-Hb and deoxy-Hb concentrations during the task (60 sec) in each channel for each subject. In particular, we focused on increases in oxy-Hb because of its superior signal-to-noise ratio (52, 53).

In the cross-sectional assessment, we compared the three groups to confirm that there were no significant differences in age and gender, using a one-way analysis of variance (ANOVA) and chi-square test, respectively. We then compared the three groups' characteristics using a one-way ANOVA to analyze differences in demographic variables. We also compared the three groups' mean oxy-Hb changes using a one-way ANOVA to analyze differences in prefrontal function. Mean Hb data were used as the dependent variable and state information was used as the independent variable. We calculated Spearman's rank correlation coefficients to examine the relationship between Hb changes during the VFT and the clinical and demographic variables (HAM-D; YMRS; GAF; duration of treatment; equivalent doses of imipramine, diazepam, chlorpromazine, lithium, and sodium valproate; age; years of education; estimated IQ; and VFT performance). For Hb data, NIRS signal is expressed as the product of hemoglobin concentration change and optical path length. Optical path length in an individual's brain region is unmeasurable, and the unit of measurement is mM • mm. We could not compare channels directly to consider the possibility that optical path length varies at an individual level. Therefore, we performed 52 one-way ANOVAs and correlational analyses for each channel, and the false discovery rate (FDR) approach was adopted to determine the significance level and prevent an increase in alpha error due to the use of multiple comparisons (54). Post hoc Tukey's tests ($p < 0.05$ per channel) were carried out on significant variables. Differences in clinical variables and drug-equivalent doses between the hypomanic and depressed BP groups were evaluated using Student's *t*-tests.

In the longitudinal assessment, clinical changes, task performance, and mean Hb changes were compared with the presence or absence of a hypomanic episode within the same individual. We performed paired *t*-tests in cases where normality was ensured by Kolmogorov–Smirnov or Shapiro–Wilk tests, and Wilcoxon sign rank tests in cases where data were skewed. Spearman's rank correlation coefficients were calculated between the Δ oxy-Hb changes and the Δ doses of medication [Hypomania (+) − Hypomania (−)] to examine the association with change over time. Significance was set at $p < 0.05$.

Results

Cross-sectional assessment

Demographic variables and clinical symptoms. Participant characteristics are shown in Table 1. Among the hypomanic patients, depressed patients, and HC groups, there were no significant differences in years of education, premorbid IQ, and task performance. Regarding medication at the time of NIRS measurement, lithium doses and chlorpromazine equivalent doses for patients in the hypomanic group tended to be larger than those in the depressed patient group ($p > 0.05$).

Comparison of Hb changes in the PFC by group. The grand-mean oxy-Hb waveforms in each group are shown in Figure 1. A one-way ANOVA revealed significant differences between groups in 12 channels (CHs 28, 29, 32, 36, 38, 39, 43–46, 49, and 50) approximately located in the bilateral DLPFC and VLPFC and in the right aTC broadly (FDR-corrected $p < 0.05$). In the multiple comparisons of the significant 12 channels, the mean oxy-Hb changes in the depressed patients were significantly smaller than those of in the HC subjects in all 12 channels (CHs 28, 29, 32, 36, 38, 39, 43–46, 49, and 50). The mean oxy-Hb changes in hypomanic patients were significantly smaller than those in HC subjects for seven channels (CHs 29, 32, 39, 43–45, and 50). Compared with HC subjects, reduced activation was commonly observed mainly in the VLPFC in both groups of BD patients. In direct comparison within BD groups, the mean oxy-Hb changes in the hypomanic patients were significantly larger than those in depressive patients in one channel (CH 49) located in the left DLPFC. Representative box plots for the three groups of significant channels are shown in Figure 2. In deoxy-Hb changes, no significant

Table 1. Characteristics of participants in the cross-sectional assessment

	Bipolar disorder		Healthy controls	
	Depressed Mean (SD)	Hypomanic Mean (SD)	Mean (SD)	p-value
Sex, male/female, n	10/6	8/3	4/8	0.133
Age, years	44.6 (8.8)	44.0 (12.6)	46.4 (6.6)	0.811
Estimated IQ	107.9 (7.2)	102.7 (10.2)	109.5 (6.8)	0.138
Education, years	15.1 (2.2)	15.3 (2.1)	15.4 (2.5)	0.969
VFT performance (words)	13.9 (4.9)	14.0 (6.2)	15.4 (5.0)	0.736
HAM-D-17	15.0 (6.0)	5.1 (4.0)		<0.001
YMRS	1.9 (1.5)	16.0 (7.8)		0.001
GAF	51.3 (13.6)	57.7 (14.1)		0.344
Duration of treatment, months	135.8 (132.7)	107.8 (139.9)		0.618
Medications				
Lithium (mg/day)	483.3 (132.9)	685.7 (226.8)		0.082
VPA (mg/day)	600.0 (200.0)	900.0 (346.4)		0.211
CBZ (mg/day)	–	250.0 (212.1)		–
Clonazepam (mg/day)	1.5 (0.7)	3		–
Lamotrigine (mg/day)	112.5 (123.8)	–		–
Imipramine eq. dose (mg/day)	124.6 (66.2)	58.3 (80.4)		0.172
CP eq. dose (mg/day)	235.6 (254.2)	496.9 (257.9)		0.053
Diazepam eq. dose (mg/day)	21.2 (12.8)	12.3 (8.5)		0.067

CBZ = carbamazepine; CP = chlorpromazine; GAF = Global Assessment of Functioning; HAM-D-17 = Hamilton Rating Scale for Depression–Revised, 17-item version; IQ = intelligence quotient; SD = standard deviation; VFT = verbal fluency task; VPA = sodium valproate; YMRS = Young Mania Rating Scale.

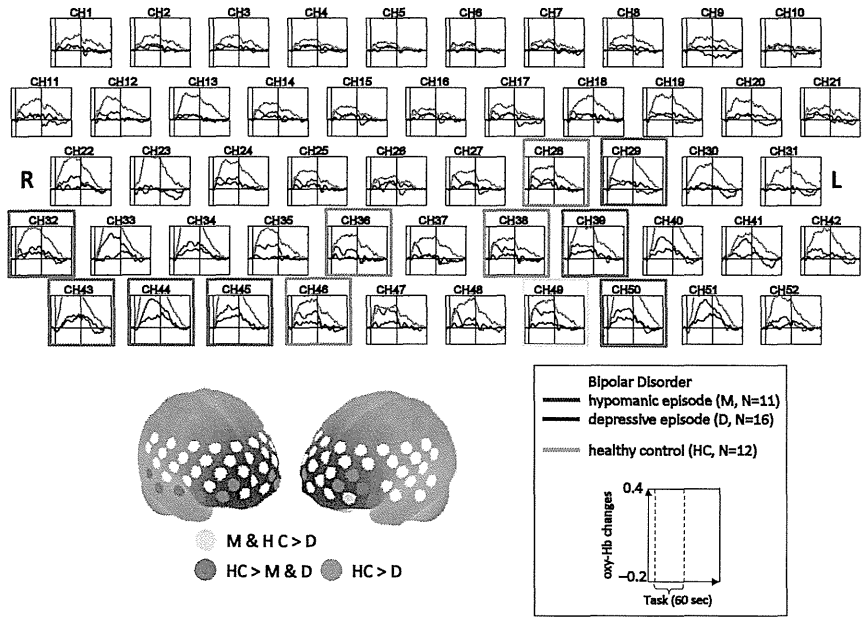

Fig. 1. The upper figures show the grand-averaged waveforms of oxygenated hemoglobin (oxy-Hb) changes during the verbal fluency task in hypomanic (red) and depressed (black) patients with bipolar disorder and healthy controls (gray). In the lower brain mapping, colored circles indicate the significant channels in one-way ANOVA [false discovery rate (FDR)-corrected $p < 0.05$]. The results of multiple comparisons are shown by color.

differences among the three groups were observed in all channels (FDR-corrected $p > 0.05$).

Correlation between NIRS signals and clinical/demographic characteristics. We found significant positive correlations between YMRS scores and mean oxy-Hb changes in all BD patients in the left DLPFC and VLPFC (CHs 49 and 50, Spearman's rho = 0.660 and 0.727, FDR-corrected $p < 0.05$) (Fig. 3). We also found negative correlations

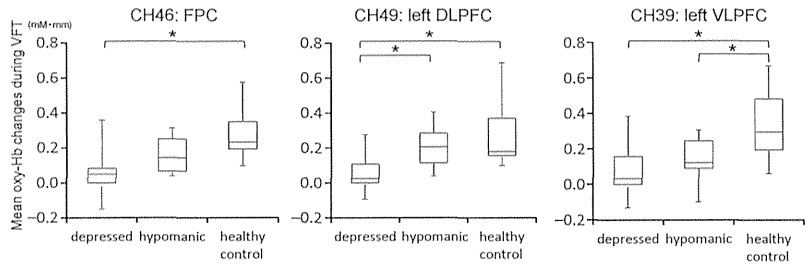

Fig. 2. Group differences in mean oxygenated hemoglobin (oxy-Hb) changes. The box plot shows mean oxy-Hb changes with 95% confidence intervals in representative significant channels. FPC = frontopolar cortex; DLPFC = dorsolateral prefrontal cortex; VLPFC = ventrolateral prefrontal cortex; VFT = verbal fluency task. *p < 0.05.

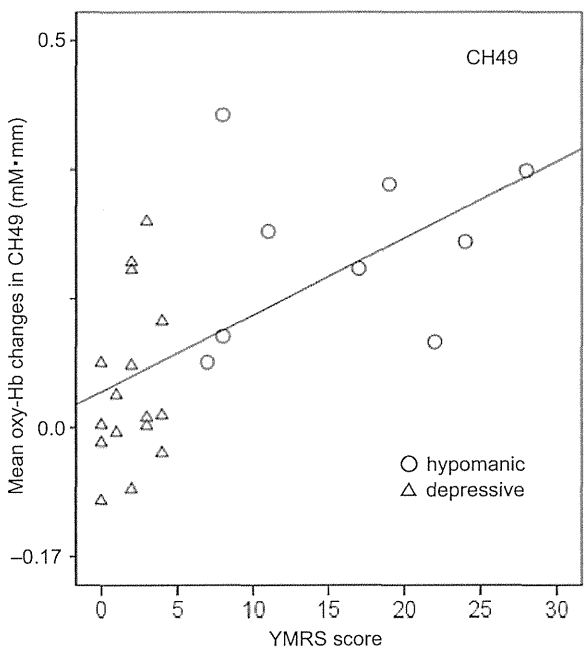

Fig. 3. Correlation with hypomanic symptom severity in mean oxygenated hemoglobin (oxy-Hb) changes during the verbal fluency task. The scatter plot illustrates a typical significant channel (CH 49) in bipolar disorder. The circles indicate hypomanic patients and the diamonds represent depressed patients. YMRS = Young Mania Rating Scale.

between YMRS scores and mean deoxy-Hb changes in all patients with BD in the FPC (CH 25, Spearman's rho = −0.706, FDR-corrected $p < 0.05$). Other variables (HAM-D, GAF, duration of treatment, age, years of education, estimated IQ, and VFT performance) were eliminated by FDR correction.

Correlation between NIRS signals and doses of medication. In order to consider the medication effects, we calculated Spearman's rank correlation coefficients between mean Hb changes and treatment doses at the time of NIRS measurement of equivalent doses of imipramine (n = 12), diazepam (n = 24), chlorpromazine (n = 17), lithium (n = 13), and sodium valproate (n = 7). For the mean oxy-Hb changes, significant correlations (uncorrected $p < 0.05$) were revealed between equivalent doses of imipramine and CH48 (rho = 0.660), chlorpromazine and CH30 (rho = 0.611) and CH40 (rho = 0.518), and sodium valproate and CH10 (rho = −0.898) and CH19 (rho = −0.767), while no significant correlation was observed after the FDR correction.

In the mean deoxy-Hb changes, a tendency toward significance (uncorrected $p < 0.05$) was revealed between the equivalent doses of imipramine and CH20 (rho = 0.708) and CH36 (rho = −0.731); diazepam and CH13 (rho = 0.446) and CH42 (rho = −0.446); chlorpromazine and CH49 (rho = −0.490); lithium and CH11 (rho = 0.716); and sodium valproate and CH11 (rho = 0.767) and CH19 (rho = −0.898); however, no significant correlation was observed after FDR correction. Other variables regarding medication and Hb changes were eliminated by uncorrected $p < 0.05$.

Longitudinal assessment of the hypomanic group

Clinical symptom changes. The mean measurement interval was 14.4 months (SD = 8.9 months, range: 2–29 months). Changes in patient symptoms and clinical characteristics are shown in Table 2. Of the eight patients who participated in the follow-up assessment, four were euthymic and four patients were depressed at the second NIRS measurement. YMRS scores were significantly decreased in the second NIRS measurement compared to the first. Regarding medication at the time of NIRS measurement, lithium doses were significantly larger when hypomanic symptoms were present (+) than when they were absent (−). No differences were found in the other variables between the two NIRS measurements.

Temporal Hb changes in the PFC. Mean oxy-Hb changes were significantly larger when hypomanic

Table 2. Characteristics of participants in the longitudinal assessment (n = 8)[a]

	Hypomanic (−) Mean (SD)	Hypomanic (+) Mean (SD)	p-value
HAM-D-17	7.9 (6.3)	6.4 (6.0)	0.64
YMRS	3.1 (3.2)	18.1 (5.4)	<0.01
VFT performance	13.8 (6.3)	13.8 (6.3)	1.00
CP eq. dose (mg/day)[b]	536.4 (598.0)	686.8 (394.4)	0.44
Imipramine eq. dose (mg/day)[b]	7.1 (18.9)	0 (0)	0.36
Diazepam eq. dose (mg/day)[b]	14.1 (10.0)	17.9 (7.4)	0.21
Lithium (mg/day)[c]	666.7 (163.3)	833.3 (81.6)	0.04

CP = chlorpromazine; HAM-D-17 = Hamilton Rating Scale for Depression–Revised, 17-item version; VFT = verbal fluency task; YMRS = Young Mania Rating Scale.
[a]Lamotrigine, clonazepam, carbamazepine, sodium valproate (n < 3).
[b]n = 7.
[c]n = 6.

symptoms were present (+) compared to when they were absent (−) in eight channels located approximately in the FPC and DLPFC (CHs 9, 14, 24, 28, 36, and 47–49, p = 0.005–0.046). The representative longitudinal changes within subjects are shown in Figure 4. Mean deoxy-Hb changes when hypomanic symptoms were present (+) were significantly smaller than those when symptoms were absent (−) in two channels located in the temporal region (CHs 11 and 32, p = 0.036).

Correlation between temporal Hb changes and dose changes of medication. Significant differences were observed between the differences in mean Hb changes and changes in medication dosage based on hypomanic symptoms [present (+) or absent (−)], as follows: Δ oxy-Hb, Δ equivalent doses of chlorpromazine and CHs 1, 11, 16, and 23; Δ equivalent doses of diazepam and CHs 2, 10, and 32; Δ doses of lithium and CH 45; Δ deoxy-Hb: Δ equivalent doses of chlorpromazine and CHs 5 and 24). Other variables for medication (oxy-Hb: Δ equivalent doses of imipramine; deoxy-Hb: Δ equivalent doses of imipramine, Δ equivalent doses of diazepam, and Δ doses of lithium) and channels were eliminated by p < 0.05. No significant correlations were found in the significant channels for the comparison of mean oxy-Hb changes in hypomanic symptoms (+) with those in hypomanic symptoms (−).

Discussion

This study used a combination of cross-sectional and longitudinal assessments to characterize state-dependent changes in hemodynamic response associated with cognitive activation in individuals with BD. The comparison of prefrontal activation between the two BD groups and the HC group revealed that both BD groups exhibited significantly smaller activation in the VLPFC during the VFT. Within the BD group, the activation of oxy-Hb changes in the hypomanic patients was significantly larger than that of the depressed patients in the left DLPFC. In addition, hypomanic symptom severity as assessed by the YMRS was positively correlated with activation in the left DLPFC and

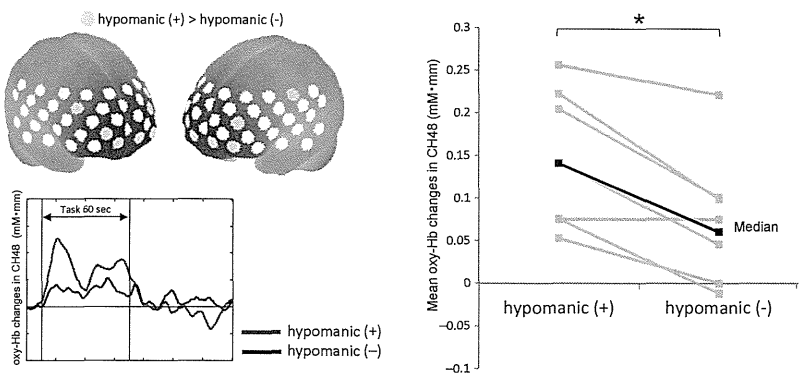

Fig. 4. Temporal changes in prefrontal activation after the resolution of hypomanic symptoms. In the left-upper brain mappings, yellow circles indicate the significant channels using Wilcoxon signed-rank tests between hypomanic-present (+) and hypomanic-absent (−) symptoms in bipolar disorder (uncorrected p < 0.05). The lower-left graph shows the grand-averaged oxygenated hemoglobin (oxy-Hb) waveforms of a typical significant channel (CH 48). The red lines indicate hypomanic (+) and the black lines indicate hypomanic (−) patients. The right line chart shows the mean oxy-Hb changes in the two near-infrared spectroscopy (NIRS) measurements for each patient. The values of the first and second NIRS measurements for each patient are connected by gray lines. The bold black line shows the median value. In CH48, oxy-Hb data for one patient were excluded because they showed a noisy waveform when hypomanic symptoms were present (+). Therefore, the statistical analysis for CH48 was performed using data from seven patients.

FPC in patients with BD. Furthermore, the longitudinal assessment in hypomanic patients revealed that prefrontal activation was decreased in the absence of hypomanic symptoms.

Hypofrontality during an executive function task in BD

Previous studies have consistently found reduced activation in the PFC, mainly the VLPFC, during executive dysfunction across mood states compared with HCs (12, 24–28, 55, 56). Neuropsychological examination also has shown worse performance in both hypomanic/manic and depressed patients compared with HCs (57). The VLPFC and the anterior cingulate cortex play an important role in cognitive reappraisal and emotional regulation (58). Functional neuroimaging studies have found decreased activation in the VLPFC across mood states (11–13). These results suggest that VLPFC hypoactivation during executive functions may be a common characteristic of symptomatic patients with BD.

Association between NIRS signals and mood states

In the first cross-sectional assessment, we demonstrated that left DLPFC activation in depressed patients was significantly lower than that in hypomanic patients. Some studies examining mood-state differences in brain functioning using a color–word Stroop or emotion face task have shown abnormalities in prefrontal functioning in BD across mood states compared to HC groups (12, 59). However, other neuroimaging studies using verbal fluency or language tasks in patients with BD have demonstrated reduced PFC activation in euthymic patients compared to HCs (56, 60), while others found larger activation in euthymic patients compared to HCs (14, 61). In addition, state-related changes in the PFC also were identified within BD, though hypo- or hyperfrontality depended on the task (12, 59, 62). Moreover, a review of longitudinal studies in neuroimaging and neuropsychological tests in BD has pointed out that brain function was altered according to illness phase (e.g., active or in remission) and mood state (e.g., manic, depressed, or euthymic) (3). Thus, it can be concluded that the PFC (DLPFC in particular) shows different activity in individuals with BD depending on their mood state.

Hypomanic symptoms and the left DLPFC

We found that patients with hypomanic symptoms exhibited increased activation during the VFT in the left DLPFC and FPC compared to patients with depressive symptoms in the cross-sectional assessment and patients without hypomanic symptoms in the longitudinal assessment. Correlational analyses also showed an association between left DLPFC function and hypomanic symptoms. Our results are comparable with past research that found FPC activation during a response inhibition task (63) and increased connectivity within the left inferior frontal gyrus (35) only in manic states.

The DLPFC demonstrates structural and functional connectivity with other PFC subregions as well as the temporal cortex, parietal cortex, thalamus, striatum, and hippocampus, and plays a role in the top-down regulation of thought and behavior (64). Patients with focal DLPFC damage are known to present volitional and behavioral disturbances such as decreased spontaneous speech, apathy, lowering of motivation, fatigability, and depressive symptoms (65). A recent NIRS study in healthy adults found an association between high apathy scores and small oxy-Hb changes in the left PFC during a VFT (66). In addition, patients with affective disorders have revealed relatively decreased activation in the left DLPFC during depressive episodes (32). In contrast, during hypomanic episodes, patients exhibit symptoms of increased activity and rapid speech as well as elevated and/or irritable mood, grandiosity, and reduced need for sleep. This suggests that DLPFC function might be relatively intact during an executive task, leading BD patients to be more talkative and energetic during hypomanic episodes.

Effects of medication on prefrontal activation

The differences in prefrontal functioning across mood states may also be explained by the effects of medication. Specifically, our data showed a tendency for hypomanic patients to be prescribed higher doses of lithium than depressed patients in the cross-sectional assessment; the longitudinal follow-up assessment indicated a similar trend. Neuroimaging studies of medication effects on individuals with BD have shown increased gray matter volume with lithium medication (including in the amygdala and anterior cingulate gyrus), suggesting a potentially neuroprotective effect of lithium (67). Acute mania is associated with elevated glutamate/glutamine levels in the left DLPFC (68), and lithium treatment is known to reduce glutamatergic overstimulation and protect neurons against excitotoxicity (69). Another study has shown decreased left IFG activation after lithium medication in euthymic patients (70). These studies suggest a transient increase in left DLPFC activation with increased lithium dosage. Patients in the

present study were recruited from a clinical setting, and we did not set criteria for medication. Even though not all patients took lithium, and we confirmed that the correlation between medication dose and NIRS signal was not significant both in the cross-sectional and longitudinal assessments, we could not completely rule out the possibility that decreased activation after the resolution of hypomanic symptoms was caused by psychotropic medication. Medication effects are one of the most important considerations when exploring the neural underpinnings of executive dysfunction in BD.

Prefrontal activation and task performance

In the present VFT, task performance was similar among groups in the cross-sectional assessment and the longitudinal follow-up assessment, and no significant correlations were found between task performance and YMRS total scores (rho = 0.074, p = 0.727). This indicates that participants in the present study could perform the VFT regardless of the severity of their hypomanic symptoms. The present VFT design was modified from an original neuropsychological test used in clinical settings. In this modified version of the VFT, the assigned syllables were changed every 20 sec during the 60-sec task period because of the reduction of time during which the subjects were silent (30). Therefore, this modified VFT was easy for the participants, and they showed similar performance. Differences in prefrontal activation among the groups with similar task performance suggest that the groups differed in their neural processing of the task demand to generate the appropriate words. In addition, the present study and previous NIRS studies using this VFT design found no significant correlation between prefrontal activation and the number of correct words generated by a participant during task performance (19, 30, 44). Moreover, previous NIRS studies that used this modified VFT showed lower activation during the VFT in patients with major depressive disorder (19) and BD (30) relative to HCs. Thus, we consider the larger prefrontal activation during the modified VFT adopted in this study as an indicator of good prefrontal function.

Limitations

This study has some limitations. First, NIRS measures only the surface area of the brain; therefore, we could not measure activity in deep brain structures such as the limbic system. Secondly, the number of study participants, particularly in the longitudinal follow-up assessment, was relatively small. For this reason, these findings cannot be generalized to a broader population of patients based on this study alone. Thirdly, as discussed previously, all patients were taking medication at the time of the NIRS measurements. Fourthly, patients with BD in the present study might be heterogeneous, with a wide range of individual differences. Because we focused on hypomanic symptoms and prefrontal functioning, we analyzed the combined BD subtypes. However, previous studies have revealed differences between BD-I and BD-II in quality of life (71), cognitive impairment (4), and brain metabolism (72). Larger-scale follow-up studies are required to confirm our results. Fifthly, we could not rule out the possible effects of psychotropic medications, as pointed out above. According to a review on the effects of medication on neuroimaging findings in BD, the majority of studies found that medication effects are not likely responsible for the differences observed between patients with BD and HCs (73). However, the absence of a significant correlation does not mean there was no effect. Further studies are needed to consider individual drugs with a sufficient number of patients at an earlier stage of BD. Finally, the present study design did not set up a healthy control group for the longitudinal assessment, and we could not entirely rule out the possibility of repetition effects of NIRS measurement; previous studies have confirmed longitudinal stability on a monthly basis in healthy adults (21–23).

Conclusions

In conclusion, using NIRS, we found a state-dependent change in prefrontal hemodynamic responses associated with cognitive activation in BD. The current data provide valuable insights into prefrontal functioning during hypomanic states, and suggest that NIRS measurement may be a useful tool for objectively evaluating state-dependent characteristics of prefrontal hemodynamics in BD. However, the present results are preliminary; future research should explore medication effects in large samples.

Acknowledgements

We would like to thank the participants in this study, as well as Ms. Tomoe Higuchi, Ms. Tamiko Yasui, Ms. Tomoe Uchiyama, and Ms. Akiko Tsurumi, who provided support for the NIRS measurements. We are also grateful for the cooperation of the staff of Tokyo Metropolitan Matsuzawa Hospital. This study was supported by the Ministry of Health, Labour, and Welfare (Health and Labour Science Research Grants for Comprehensive Research on Disability, Health, and Welfare,

H23-seishin-ippan-002) (YN and TO); an Intramural Research Grant (23-10 and 26-3) for Neurological and Psychiatric Disorders of NCNP (YN and TO); the JSPS/MEXT [Grant-in-Aid for Scientific Research on Innovative Areas (Comprehensive Brain Science Network and Adolescent Mind & Self-Regulation; 23118001 and 23118004)] to KK; and the Takeda Science Foundation (YN). This work was partly the result of the 'Development of biomarker candidates for social behavior' project carried out under the Strategic Research Program for Brain Sciences by the MEXT.

Disclosures

YO (Tokyo Metropolitan Matsuzawa Hospital) has a potential conflict of interest in the submitted work. The Tokyo Metropolitan Matsuzawa Hospital has had an official contract with the Hitachi Group (Advanced Research Laboratory, Hitachi, Ltd., and The Research and Developmental Center, Hitachi Medical Corporation) for a collaborative study of the clinical application of NIRS in psychiatric disorders. For this study, the Hitachi Group provided a project grant (JPY 300,000/year) and material support [temporary rental of an NIRS (Optical Topography) ETG-4000 system]. YN, KT, TO, RI-S, and KK have no relevant conflicts of interest to report.

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