ウェブサイト公開用

（様式 10）
（海外特別研究員事業）
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海 外 特 別 研 究 員 最 終 報 告 書

独立行政法人日本学術振興会 理事長　殿

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受 付 番 号　201860411
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（氏名は必ず自署すること）

海外特別研究員としての派遣期間を終了しましたので、下記のとおり報告いたします。
なお、下記及び別紙記載の内容については相違ありません。

記

1. 用務地（派遣先国名）用務地：　オクラホマ州　（国名：　米国　）

2. 研究課題名（和文）※研究課題名は申請時のものと違わないように記載すること。
　ニューロフィードバックで安静時脳機能結合は変化するか？:脳波―fMRI 同時計測

3. 派遣期間：平成　30 年　4 月　1 日　～　令和　2 年　3 月　31 日

4. 受入機関名及び部局名
　オクラホマ大学　生体医工学スティーブンソン校

5. 所期の目的の遂行状況及び成果…書式任意　**書式任意（A4 判相当 3 ページ以上、英語で記入も可）**
（研究・調査実施状況及びその成果の発表・関係学会への参加状況等）
（注）「6. 研究発表」以降については様式 10－別紙 1～4 に記入の上、併せて提出すること。

OVERVIEW

Not a few types of research have elucidated that psychiatric disorders are disorders of brain circuitry, and modulating altered brain circuitry will be an effective treatment for mood and anxiety disorders. The purpose of this fellowship was to learn how to conduct simultaneous EEG-fMRI experiments, and investigating the mechanism of neurofeedback training regulating the brain circuitry, so it functions in a healthier manner. As an overseas research fellow, I started intensive training for EEG and fMRI studies. Since my research topic was Obsessive-Compulsive Disorder and Autism Spectrum Disorder, I have been interested in cognitive inflexibility and repetitive thinking, in other words, ‘stacked’ mind. I contributed to a proof-of-concept study related to real-time fMRI-neurofeedback (rtfMRI-NF) targeting repetitive negative thinking and rumination. In addition, I have conducted EEG-fMRI neurofeedback experiments targeting the amygdala and ventromedial prefrontal cortex (vmPFC) for mood and anxiety disorders. One paper designing a novel rtfMRI-NF targeting rumination, one paper investigating the efficacy of rtfMRI-NF vmPFC training, and one paper related to EEG microstates have been published with me as a co-author. Eight conference papers related to EEG and fMRI study have been accepted, and two papers are in preparation.

1. Misaki M, **Tsuchiyagaito A**, Al Zoubi O, Paulus M, Bodurka J. Connectome-wide search for functional connectivity locus associated with pathological rumination as a target for real-time fMRI neurofeedback intervention. Neuroimage Clin. 2020 Mar 12;26:102244. PubMed PMID: 32193171; PubMed Central PMCID: PMC7082218.
2. Mayeli A, Misaki M, Zotev V, **Tsuchiyagaito A**, Al Zoubi O, Phillips R, Smith J, Stewart JL, Refai H, Paulus MP, Bodurka J. Self-regulation of ventromedial prefrontal cortex activation

using real-time fMRI neurofeedback-Influence of default mode network. Hum Brain Mapp. 2020 Feb 1;41(2):342-352. doi: 10.1002/hbm.24805. Epub 2019 Oct 21. PubMed PMID: 31633257.

3. Al Zoubi O, Mayeli A, **Tsuchiyagaito A**, Misaki M, Zotev V, Refai H, Paulus M, Bodurka J and the Tulsa 1000 Investigators (2019) EEG Microstates Temporal Dynamics Differentiate Individuals with Mood and Anxiety Disorders From Healthy Subjects. Front. Hum. Neurosci. 13:56. doi: 10.3389/fnhum.2019.00056
4. **Tsuchiyagaito A**, Misaki M, Smith J, Paulus M, Bodurka J. *A Connectivity-Based Real-Time fMRI Neurofeedback Targeting the Rumination.* Accepted for poster presentation, OHBM 2020 - Annual Meeting Organization for Human Brain Mapping (Montreal, Québec, Canada; June 2020).
5. **Tsuchiyagaito A**, Smith J, El-Sabbagh N, Mayeli A, Zotev V, Misaki M, Paulus M, Bodurka J, Savitz J. *FMRI Neurofeedback Amygdala Training Influences Immune Responses*. Accepted for poster presentation, OHBM 2020 - Annual Meeting Organization for Human Brain Mapping (Montreal, Québec, Canada; June 2020).
6. **Tsuchiyagaito A**, Mayeli A, Al Zoubi O, Misaki M, Zotev V, Bodurka J. *How Many Sessions Needed for fMRI Neurofeedback Training to Increase Amygdala Activity and to Influence Functional Connectivity?* Accepted as a poster presentation at Society of Biological Psychiatry's 2019 Annual Meeting (Chicago, IL; May 2019).
7. **Tsuchiyagaito A**, Misaki M, Mayeli A, Zotev V, Al Zoubi O, Paulus M, Aupperle R, Bodurka J. *Targeted vmPFC Modulation with fMRI Neurofeedback Changes Functional Connectivity in Depression.* Accepted as a poster presentation at Society of Biological Psychiatry's 2019 Annual Meeting (Chicago, IL; May 2019).
8. Mayeli A, Al Zoubi O, Misaki M, **Tsuchiyagaito A**, Refai H, Paulus M, Bodurka J. *Simultaneous EEG-fMRI-Eye Tracker Measurements for Determining Subject's Vigilance during Resting-State fMRI.* Accepted as a poster presentation at Society of Biological Psychiatry's 2019 Annual Meeting (Chicago, IL; May 2019).
9. Misaki M, **Tsuchiyagaito A**, Al Zoubi O, Paulus M, Bodurka J. Brain regional connectome-wide search identified a resting-state functional connectivity locus within precuneus associated with rumination symptom severity in mood and anxiety disorders. Accepted as a poster presentation at International Society for Magnetic Resonance in Medicine 27th Annual Meeting (Montreal, QC, Canada; May 2019).
10. Al Zoubi O, Mayeli A, Misaki M, Zotev V, **Tsuchiyagaito A**, Tulsa 1000 Investigators, Refai H, Paulus M, Bodurka J. *BOLD Representation of Canonical EEG Microstates.* Accepted as a poster presentation at International Society for Magnetic Resonance in Medicine 27th Annual Meeting (Montreal, QC, Canada; May 2019).
11. Mayeli A, Al Zoubi O, Misaki M, **Tsuchiyagaito A**, Refai H, Paulus M, Bodurka J. Simultaneous EEG-fMRI-Eye Tracker Study for Measuring Subject's Vigilance during Resting-State fMRI. Accepted as a poster presentation at Organization for Human Brain Mapping's 2019 Annual Meeting (Roma, Italy; June 2019).

MAIN PROJECT: Developing the novel neurofeedback method using fMRI and EEG

Repetitive negative thinking (RNT): transdiagnostic key symptom.

Rumination, worry, and other forms of uncontrolled repetitive negative thinking (RNT) are fundamental to the distress and impairment experienced by patients with mood and anxiety disorders (MAD). Studies have shown that RNT is consistently related to greater frequency, duration and severity of depressive episodes. Given the strong overlap between depression and anxiety, RNT began receiving more attention as a factor potentially involved in the development of

anxiety. Further investigation has supported the role of RNT as a transdiagnostic risk factor; that is, RNT seems to increase risk both for depression and anxiety.

Neurofeedback (NF): a possible treatment for RNT. Brain-based therapies such as real-time fMRI-neurofeedback (rtfMRI-NF) can target underlying neurofunctional deficits implicated in clinical symptoms and is a promising way to treat MAD. However, there are relatively few brain therapy studies focusing transdiagnostic symptoms. Up to now, the neural correlates of RNT have not been excessively explored, and RNT-specific target regions for rtfMRI-NF remain to be determined. Posterior cingulate cortex and precuneus (PCC/precuneus) are associated with internal self-oriented thought, and its hyperactivity in resting-state is often reported for patients with MAD; however, PCC/precuneus are not homogeneous regions and which specific parts of the PCC/precuneus are responsible for pathological RNT needs to be investigated. Moreover, PCC/precuneus plays a crucial role in switching between the default mode network (DMN) and the task-positive network, and its function is unique among other regions related to DMN (Fig.1).

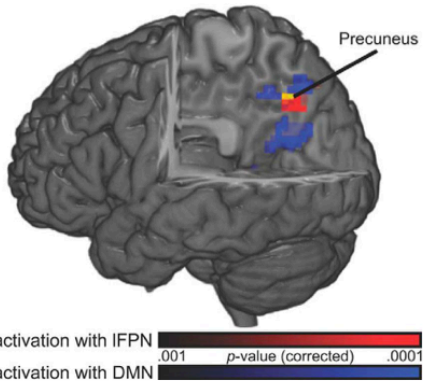

Figure 1. Areas within precuneus exhibited task-dependent connectivity with lFPN (red) and DMN (blue) [Adopted by Utevsky et al., 2016]. Strikingly, a subregion in the precuneus (coordinates: 6, -63, 42; yellow) differentiated task states in both networks, indicating that this region is a shared node between multiple networks. lFPN: executive control, left frontoparietal network; DMN: default mode network.

STUDY01: Identify Target FC. We tested our preliminary hypothesis that MAD individuals would have: (1) functional alterations within PCC/precuneus compared to HC; and (2) distinct FC of PCC/precuneus related to an important facet of RNT, rumination.

Methods. The study was performed by the secondary data analysis of a large naturalistic sample (Tulsa 1000; T1000 study). We conducted a brain regional connectome-wide approach to search the region within the PCC/precuneus having FC associated with the Ruminative Responses Scale (RRS). A whole-brain connectivity analysis using multivariate distance matrix regression (MDMR) was performed for the seed voxels within a target area.

Results. MDMR analysis found a significant interaction effect of group×RRS (p<0.005) in the precuneus. No other significant effect was found. A post-hoc analysis revealed that FC between the precuneus and the bilateral temporoparietal junction (TPJ) had a significant interaction effect (p<0.001 and cluster-size p<0.05). Connectivity between the precuneus and TPJ had significant positive correlation with RRS for MAD (leftTPJ; t[263]=4.82, p<0.001, rightTPJ; t[263]=4.94, p<0.001) but not for HC.

Conclusion. We found that the correlation between rumination measured by RRS and precuneus-TPJ FC were different between MAD and HC (correlation was positive for MAD and negative for HC). Precuneus and TPJ are associated with self-referential processing evident in RNT, and those regions might be involved in exceeded self-focused attention in ruminative individuals.

Publication. There results were published: Misaki M, **Tsuchiyagaito A**, Al Zoubi O, Paulus M, Bodurka J. Connectome-wide search for functional connectivity locus associated with pathological rumination as a target for real-time fMRI neurofeedback intervention. Neuroimage Clin. 2020 Mar 12;26:102244. PubMed PMID: 32193171; PubMed Central PMCID: PMC7082218.

STUDY02: Proof-of-concept Study to Test rtfMRI-NF Targeting Rumination. We established the novel NF method targeting precuneus-RTPJ connectivity to improve rumination based on the preliminary study (see above). The purpose of this NF study is to investigate whether healthy

subjects can learn how to modulate brain connectivity between precuneus-RTPJ; which is related to pathological rumination.

Methods. This proof-of concept study utilized connectivity-based rtfMRI-NF (cnf) to normalize brain FC associated with rumination. Healthy participants were instructed to decrease FC between the precuneus and the right temporoparietal junction (rTPJ), associated with high levels of rumination, while engaging in a self-referential task. Details of this rtfMRI-NF design were shown in Figure 2.

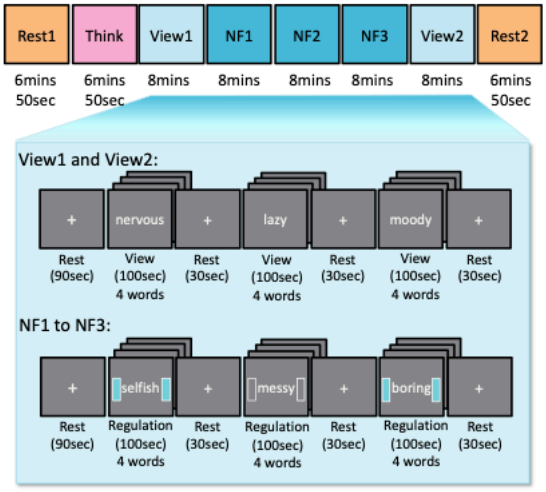

Figure 2. Experimental design. A neurofeedback session contains a first resting scan (Rest1), rumination-inducing task scan (Think), followed by five experimental runs: View1, Neurofeedback 1 to 3 (NF1 to 3) and View2, and ended with a last resting scan (Rest2). Each experimental run started with a first 'Rest' block (90-sec), followed by 'View' or 'Regulation' block (100-sec) during presentation of four negative trait words (25-sec for each word) and 'Rest' block (30-sec) alternatively

Results. The cnf group (n=14) showed a linear decrease in the precuneus-rTPJ FC across neurofeedback training (trend[114]=-0.180, 95% confidence interval [CI, (-0.330,-0.0030)]), while the sham group (n=14) showed a linear increase in the target FC (trend[114]=0.151, 95% CI (0.000,0.301)). The cnf group showed a greater reduction in state-rumination compared to the sham group after neurofeedback training (p=0.03). Although de-coupled precuneus-rTPJ FC did not predict attenuated state-rumination, only in cnf group it predicted a reduction in difficulty of identifying feeling (β=1.171, p=0.03). We did not find any significant aversive effects of rtfMRI-nf in all study participants.

Conclusion. These results suggest that cnf has the capacity to influence FC among precuneus and rTPJ of a ruminative brain circuit. This approach can be applied to mood and anxiety patients to determine the clinical benefits of reduction in maladaptive rumination. We will extend these works for future rtfMRI-NF studies.

Publication. We submitted these results to an international journal.

OTHER ACHIEVEMENTS.

How many sessions needed for fMRI neurofeedback training to increase amygdala activity and to influence functional connectivity?

We examined the effect of a number of rtfMRI-NF training sessions on the abilities to increase the left amygdala (LA) activity and to influence LA resting-state functional connectivity (rsFC). Increased LA activity and reduced self-reported depression and anxiety were evident in the first rtfMRI-NF session. A single rtfMRI-NF session is sufficient for subjects to self-upregulate LA activity, with the effect on rsFC observed in later training sessions. This suggests that the training effect on intrinsic brain activation could persist after the first successful upregulation of LA activity.

Publication. These results were published as a conference paper: **Tsuchiyagaito, A.**, Mayeli, A., Al Zoubi, O., Misaki, M., Zotev, V., & Bodurka, J. (2019). F75. How Many Sessions Needed for fMRI Neurofeedback Training to Increase Amygdala Activity and to Influence Functional Connectivity?. *Biological Psychiatry*, *85*(10), S241-S242.

Targeted vmPFC Modulation with fMRI Neurofeedback Changes Functional Connectivity in Depression.

The vmPFC is part of the default mode network (DMN), serves an important role in processing emotion, and is implicated in many psychiatric disorders. We examined the effect of rtfMRI-nf modulation of the vmPFC, and assessed training effects on resting-state functional connectivity (rsFC). The participants succeeded in vmPFC activity upregulation (effect size = 0.41, compared to 0 value), which was also associated with increased rsFC with the right thalamus, and decreased

rsFC with the left parahippocampal gyrus. The connectivity between vmPFC and limbic structures represented by the thalamus and parahippocampal gyrus was changed after just one rtfMRI-nf session. Mood improvement was correlated with connectivity between vmPFC and both executive and salient networks. Because vmPFC is part of the DMN, rtfMRI-nf vmPFC modulation has the potential to change network interactions between DMN and other brain networks.
Publication. These results were published as a conference paper: **Tsuchiyagaito, A.**, Misaki, M., Mayeli, A., Zotev, V., Al Zoubi, O., Paulus, M., Aupperle, R., & Bodurka, J. (2019). T144. Targeted vmPFC Modulation With fMRI Neurofeedback Changes Functional Connectivity in Depression. *Biological Psychiatry*, *85*(10), S185.