様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

# 科学研究費助成事業　　研究成果報告書

令和　５ 年　 ６ 月 ２０ 日現在

機関番号：１５４０１
研究種目：基盤研究(C)（一般）
研究期間：2020～2022
課題番号：２０Ｋ０７７２３

研究課題名（和文）A social defeat model to identify neural markers of human depression vulnerability

研究課題名（英文）A social defeat model to identify neural markers of human depression vulnerability

研究代表者

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交付決定額（研究期間全体）：（直接経費）　　2,800,000円

研究成果の概要（和文）：新型コロナウイルスのパンデミックと大学の制限のため、提案されたプロジェクトの一部を実施できませんでした。
社会データベースの分析により、うつ病および社交不安の症状を予測する 4 つの社会的性格特性が特定されました。これには、うつ病の症状を 1 年前に予測し、脳構造の異常と関連する社会的信頼が含まれます（Fermin et al、2022、Scientific Reports）。
私たちは、内臓情報が脳機能と精神的健康にどのような影響を与えるかを提案する理論論文（Fermin、Friston & Yamahaki、2022、Royal Society Open Science）を発表しました。

研究成果の学術的意義や社会的意義
Our analyzes of social databases and neuroimaging data revealed that social personality traits can be used as social markers to predict the development of mental health problems at least one year in advance. This finding can be used for the development of social policies to prevent health problems.

研究成果の概要（英文）：Due to the COVID pandemic and restrictions to conduct experiments with human participants we were unable to conduct part of the proposed project the experiment that would investigate the neural basis of our social defeat task. However, the other part of the project analyzed social databases and identified four social personality traits that significantly predict depressive and social anxiety symptoms: social mindfulness, self-esteem, social responsiveness and trust (published as Fermin et al, 2022, Scientific Reports). We found, for instance that reduced social trust can predict depressive symptoms one year in advance and is linked with abnormalities in brain structures.
Finally, we published on theoretical paper (Fermin, Friston & Yamawaki, 2022, Royal Society Open Science) to propose how visceral and physiological information represented in the brain insular cortex interacts other brain regions involved in social cognition to contribute to mental health.

研究分野：Neuroscience

キーワード：interoception　social cognition　social personality　biomarkers　depression　anxiety　mental health　brain structure

様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９（共通）

## １．研究開始当初の背景

(1) MDD directly impacts 4.4% of the world population leading to an estimate of 322 million currently living with MDD (WHO, 2017). The prevalence of mood disorders including MDD, anxiety and post-traumatic stress disorders exorbitantly increases to 22.1% of the population of regions with high social conflict (Charlson et al., 2019). Despite the well-known impact of aversive social interactions on human health (Rook, 2014; Pickett & Kate, 2018), little is known about the neurobiological markers that predict individual dispositions in vulnerability and resilience to depressive mood triggered by aversive social interactions.

(2) Animal models of MDD based on social defeat and learned helplessness are simple but capture similar effects of aversive social interactions humans face at home or the work place, such as harassment, abuse, social dominance and inequality (Bjorkqvist, 2001; Maier & Seligman, 2016). Animals vulnerable to MDD display higher dopaminergic and lower PFC activities, and develop higher depressive symptoms following chronic social stress. Activity and optical stimulation of areas such as medial PFC, insula and amygdala can induce resilience and reduce depressive symptoms (Muir et al., 2019; Feltes et al., 2019).

(3) Despite the generalized negative effect of learned helplessness to other contexts (Hiroto & Seligman, 1968), its neurobiological basis in humans remains elusive. Mixed-motive economic games that pose a conflict between selfish and equality choices have been used to understand human social dominance and inequality, which are social factors implicated in the etiology of MDD (Sanfey et al., 2003; Tricomi et al., 2010; Gospic et al., 2011). However, neuroeconomic studies have yet to link aversive neuroeconomic signals with MDD. The Cyberball game has been used to understand how social rejection impacts human emotional responses (Eisenberger et al., 2003; Onoda et al., 2009; Nishiyama et al., 2015). Contrary to daily-life where people can fight against aversive social interactions, in the Cyberball game participants are mere passive observers.

## ２．研究の目的

This research aimed to test a new Human Social Defeat (HSD) game created to identify the neural and interoceptive mechanisms of individual dispositions in resilience and vulnerability to depression.

Machine learning methods, structural and functional MRI and transcranial direct current stimulation were planned to identify individual dispositions and predict depressive symptoms.

## ３．研究の方法

(1) In order to identify social personality factors with predictive power of future mental health problems, specifically of mood and anxiety disorders, this research project was organized into two parts.

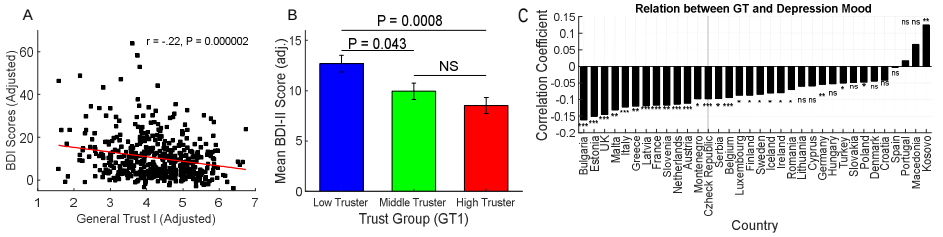
(2) In Part One, we sought to test a newly developed task, called human social defeat task (HSD task), to test participants' resilience and vulnerability to develop depressive mood in response to aversive social experiences. In the HSD task, we manipulated behavior performance, monetary incentives, and social interactions. Monetary incentives, large payoff and small payoff, were used to modulate a participant's motivation to be selfish and harm a partner or to be cooperative and help a partner. Behavior performance aimed to test reaction time so that the faster participant would be in control of the game and have the power to decide to be selfish or cooperative. Basically, the HSD task is a paradigm which requires finger pressing of a button after a cue signal. The task was planned to be conducted with a computer program as the participant's partner. In that regard, we would be able to manipulate the computer's reaction time and behavior, so that the computer partner would be the faster and selfish, always the fast and cooperative, or

always the slower. The task was also planned to be played within an fMRI scanner to order to acquire brain data and identify neural signals that predict the emergence of a participant's quasi-depressive mood while playing the task and to test whether such neural signals actually predict a participant's self-reported depressive mood, anxiety, social anxiety and stress resilience. Unfortunately, we were unable to test the HSD task due to the COVID pandemic and restrictions to run experiments with human participants.

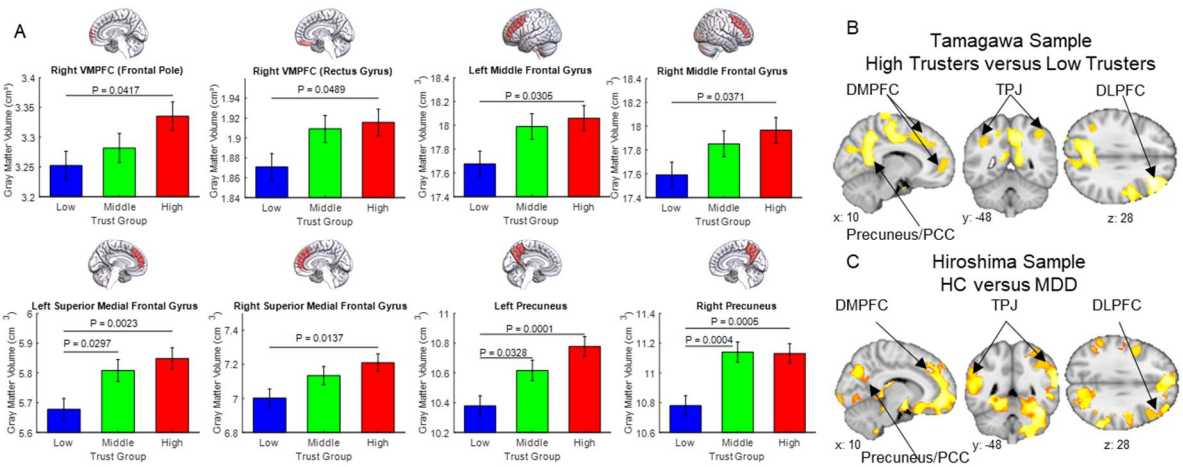
(3) In Part II of this project, we sought to investigate whether social personality traits could be used to predict individual differences in vulnerability to depression. To achieve this goal, we analyzed behavior and questionnaire data available in databases in Japan and in Europe. The Japanese database used was that of the Human Brain Sociality at the Tamagawa University and the United Kingdom (UK) Data Service. Analyzes of social personality data revealed significant results described below.

## ４．研究成果

(1) Analyzes of the Tamagawa Data, revealed that trust attitude, defined as the expectation that others will behave fairly, act lawfully and reciprocate good behavior, significantly predicted self-reported depressive symptoms one year in advance (Figure 1A); individuals classified as high trusters also showed significantly lower depressive symptoms than those in the low trust group (Figure 1B). Analysis of the UK Data Service, also revealed that lower trust was associated with self-reported depressive mood across multiple countries (Figure 1C, stars represent significant result; ns: non-significant).




(2) Analyzes of brain structure also revealed that participants in the Tamagawa data that showed lower trust also exhibited reduced volume of brain regions involved in social cognition (Figure 2A-B). The reduction of the volume of brain areas in low trusters was similar to the reduction in patients with actual depression (Figure 2C).




(3) In summary, our results revealed that individual differences in trust could be used to predict depression one year in advance. Although our participants had no clinical diagnosis of depression, the brains of low trusters showed similar reduction in volume of regions involved in social cognition, suggesting possible deficits in social cognitive functions may increase one's vulnerability to develop depression.

５．主な発表論文等

〔雑誌論文〕　計2件（うち査読付論文　2件／うち国際共著　2件／うちオープンアクセス　2件）

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|---|---|
| １．著者名<br>Fermin Alan S. R.、Kiyonari Toko、Matsumoto Yoshie、Takagishi Haruto、Li Yang、Kanai Ryota、Sakagami Masamichi、Akaishi Rei、Ichikawa Naho、Takamura Masahiro、Yokoyama Satoshi、Machizawa Maro G.、Chan Hui-Ling、Matani Ayumu、Yamawaki Shigeto、Okada Go、Okamoto Yasumasa、Yamagishi Toshio | ４．巻<br>12 |
| ２．論文標題<br>The neuroanatomy of social trust predicts depression vulnerability | ５．発行年<br>2022年 |
| ３．雑誌名<br>Scientific Reports | ６．最初と最後の頁<br>1-14 |
| 掲載論文のDOI（デジタルオブジェクト識別子）<br>10.1038/s41598-022-20443-w | 査読の有無<br>有 |
| オープンアクセス<br>オープンアクセスとしている（また、その予定である） | 国際共著<br>該当する |

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| １．著者名<br>Fermin Alan S. R.、Friston Karl、Yamawaki Shigeto | ４．巻<br>9 |
| ２．論文標題<br>An insula hierarchical network architecture for active interoceptive inference | ５．発行年<br>2022年 |
| ３．雑誌名<br>Royal Society Open Science | ６．最初と最後の頁<br>1-22 |
| 掲載論文のDOI（デジタルオブジェクト識別子）<br>10.1098/rsos.220226 | 査読の有無<br>有 |
| オープンアクセス<br>オープンアクセスとしている（また、その予定である） | 国際共著<br>該当する |

〔学会発表〕　計0件

〔図書〕　計0件

〔産業財産権〕

〔その他〕

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６．研究組織

| | 氏名<br>（ローマ字氏名）<br>（研究者番号） | 所属研究機関・部局・職<br>（機関番号） | 備考 |
|---|---|---|---|

７．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

８．本研究に関連して実施した国際共同研究の実施状況

| 共同研究相手国 | 相手方研究機関 |
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