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AUTHOR(S):

Tei, Shisei; Fujino, Junya; Itahashi, Takashi; Aoki, Yuta Y.; Ohta, Haruhisa; Kubota, Manabu; Sawajiri, Shuji; ... Takahashi, Hidehiko; Kato, Nobumasa; Nakamura, Motoaki

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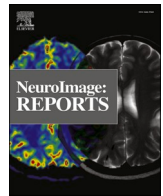
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## The right temporoparietal junction during a cooperation dilemma: An rTMS study

Shisei Tei<sup>a,b,c,d,\*\*,1</sup>, Junya Fujino<sup>a,b,e,\*,1</sup>, Takashi Itahashi<sup>a</sup>, Yuta Y. Aoki<sup>a</sup>, Haruhisa Ohta<sup>a,f</sup>,  
Manabu Kubota<sup>a,b</sup>, Shuji Sawajiri<sup>e</sup>, Ryu-ichiro Hashimoto<sup>a,g</sup>, Hidehiko Takahashi<sup>a,b,e</sup>,  
Nobumasa Kato<sup>a</sup>, Motoaki Nakamura<sup>a,h,\*\*\*</sup>

<sup>a</sup> Medical Institute of Developmental Disabilities Research, Showa University, 6-11-11 Kita-karasuyama, Setagaya-ku, Tokyo, Japan

<sup>b</sup> Department of Psychiatry, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaracho, Sakyo-ku, Kyoto, 606-8507, Japan

<sup>c</sup> Institute of Applied Brain Sciences, Waseda University, 2-579-15 Mikajima, Tokorozawa, Saitama, Japan

<sup>d</sup> School of Human and Social Sciences, Tokyo International University, 2509 Matoba, Kawagoe, Saitama, Japan

<sup>e</sup> Department of Psychiatry and Behavioral Sciences, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo, Japan

<sup>f</sup> Department of Psychiatry, School of Medicine, Showa University, 6-11-11 Kita-karasuyama, Setagaya-ku, Tokyo, Japan

<sup>g</sup> Department of Language Sciences, Graduate School of Humanities, Tokyo Metropolitan University, 1-1 Minami-Osawa, Hachioji-shi, Tokyo, Japan

<sup>h</sup> Kanagawa Psychiatric Center, 2-5-1 Serigaya, Yokohama, Kanagawa, Japan

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### ABSTRACT

Cooperation enhances interpersonal communication and nurtures society. However, efforts to socially cooperate may often evoke conflict. Individuals may selfishly pursue a greater reward or success by exploiting the efforts of other individuals or taking unnecessary risk to oneself. Such a cooperation dilemma is highly prevalent in real life; thus, it has been studied in various disciplines. Although published functional magnetic resonance imaging studies have shown the involvement of the right temporoparietal junction (TPJ) in resolving a dilemma through cooperation, a causal relationship between the two has rarely been explored. Hence, we investigated this issue by combining repetitive transcranial magnetic stimulation with a priority game task (modified snowdrift game). In this game task, participants and opponent players jointly faced a problem whereby their collaboration was anticipated to defuse the situation. This conflicted with a choice in the participant's self-interest that was more rewarding but risky. We further included conditions with and without explicit social cues using figures describing elderly/pregnant passengers in the game opponent's car, and measured participants' prosocial traits to examine any cue-induced effect as well as the personality-cooperation relationship, respectively. The cooperation ratio was not statistically different in both the no-cue and with-cue conditions between the sham stimulation and inhibitory continuous theta burst stimulation (cTBS). However, after cTBS, in the no-cue condition, the strength of the association between cooperation ratio and empathy traits decreased significantly. These results add to our knowledge about the right TPJ's role in social cognition, which may be extraordinarily complex. This topic is deserving of further examination.

### 1. Introduction

Cooperation is at the heart of our lives, enhancing interpersonal communication and nurturing society (Abe et al., 2019; Fehr and

Schmidt, 1999; Hari et al., 2015; Rand et al., 2014). We share food, goods, and physical efforts with others to help ourselves adjust to situational demands (Dunbar, 1998). When we recognize others in need, we often become motivated to cooperate by overcoming selfishness (Fehr

\* Corresponding author. Medical Institute of Developmental Disabilities Research, Showa University, 6-11-11 Kita-karasuyama, Setagaya-ku, Tokyo, Japan.

\*\* Corresponding author. Medical Institute of Developmental Disabilities Research, Showa University, 6-11-11 Kita-karasuyama, Setagaya-ku, Tokyo, 157-8577, Japan.

\*\*\* Corresponding author. Medical Institute of Developmental Disabilities Research, Showa University, 6-11-11 Kita-karasuyama, Setagaya-ku, Tokyo, Japan.

E-mail addresses: [chengctky@gmail.com](mailto:chengctky@gmail.com) (S. Tei), [jf15psyc@tmd.ac.jp](mailto:jf15psyc@tmd.ac.jp) (J. Fujino), [motoaki@motoaki.com](mailto:motoaki@motoaki.com) (M. Nakamura).

<sup>1</sup> These authors contributed equally to this work.

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and Fischbacher, 2004). On the other hand, people may also selfishly put themselves at risk or pursue greater benefits by exploiting someone else to achieve their own success (Kummerli et al., 2007). Such a cooperation dilemma is highly prevalent in real life; thus, it has been studied in various disciplines including evolutionary biology, social psychology, and behavioral economy. A better understanding of the mechanisms of how we cooperate by overcoming selfishness can provide significant insights into human social behavior.

Previously published functional magnetic resonance imaging (fMRI) research has indicated that the temporoparietal junction (TPJ) plays an important role in decision-making in a cooperation dilemma. During a variety of tasks in economic games presenting a cooperation dilemma, a strong link has been reported between task-dependent TPJ activation and cooperative choices (Baumgartner et al., 2012; Morishima et al., 2012; Fukui et al., 2006). However, a causal relationship between the two has not been sufficiently examined. To study this relationship, repetitive transcranial magnetic stimulation (rTMS) is one of the most promising techniques (Beynel et al., 2020; Bukowski et al., 2020; Kuhnke et al., 2020; Obeso et al., 2018). Indeed, a recent rTMS study elegantly demonstrated the causal role of the right TPJ in prosocial decision-making by shifting away from a self-centered perspective (Soutschek et al., 2016). In that study, inhibition of the right TPJ resulted in a reduced ability to consider the perspectives of other participants. It also reduced the willingness to be cooperative, as examined by social/temporal discounting and visual perspective-taking tasks (Soutschek et al., 2016). However, due to the paucity of rTMS studies on this issue, it remains unclear how right TPJ functioning is involved in cooperative dilemmas in daily social exchange settings where people tend to prefer collaboration due to its situational context.

A priority game task, such as the snowdrift game task, has been widely used to examine peoples' decision-making in situations presenting cooperative dilemmas (Kummerli et al., 2007; Qi et al., 2015; Zhang et al., 2018). In the snowdrift game task, participants and opponent players jointly face a problem whereby their collaboration is expected to resolve the situation together. This response is contrasted with a choice in self-interest that is more rewarding and efficient but risky (Kummerli et al., 2007). More specifically, if two car drivers are trapped on opposite sides of a snowdrift, they are expected to shovel together to clear a path (i.e., shared gain via cooperation), even if they do not know each other (Kummerli et al., 2007). In this situation, one driver often chooses to shovel by themselves to open the snowdrift, even the other driver cannot shovel at all (e.g., being injured). Meanwhile, the first driver might be able to pass through more easily without shoveling, but this can risk more trouble (being stuck for longer) when the other driver does not shovel either (Kummerli et al., 2007). As such, given that situations similar to snowdrift examples are ubiquitous in people's working environment, the snowdrift game can more naturally and sensitively measure participants' preferences for cooperation between the collaborators to reach shared/essential benefits compared to conventional game tasks (see Methods and Supplementary Methods).

In the current study, we aimed to investigate the causal role of the right TPJ during a cooperative dilemma combining rTMS and the priority game task (a modified snowdrift game task; MSG task). Before conducting the MSG in healthy volunteers, we applied either neuro-navigated inhibitory continuous theta-burst stimulation (cTBS) (Huang et al., 2005) or sham stimulation over the right TPJ. Previous studies have highlighted that the explicit grasp of situational context affects cooperative decision-making (Bear and Rand, 2016; Spitzer et al., 2007). Therefore, based on the previous studies (Vanmarcke et al., 2017), the current MSG task included two conditions with or without figures showing elderly and pregnant passengers in the game opponent's car to study how such explicit social cues could influence a participant's cooperative decision associated with TPJ activity. In addition, it has been reported that individual differences in pro-sociality were associated with cooperative behavior (Gonzalez-Liencrees et al., 2013). Thus, we quantified participants' empathic and altruistic traits (Davis, 1985;

Rushton et al., 1981), and we exploratively performed correlation analyses between these scores and the level of cooperation in the MSG task. We hypothesized that the right TPJ functioning would be critically involved in cooperative decision-making. Specifically, we predicted that the level of cooperation ratio in the MSG would decrease after cTBS of the right TPJ. Moreover, we also hypothesized that after cTBS, the strength of the relationship between the cooperation ratio and prosocial traits of participants would show a decrease due to changes in the activation of this brain area (Mottaghy et al., 2003; Li et al., 2017).

## 2. Methods

### 2.1. Participants

Twenty-five healthy male volunteers were enrolled in this study. We only recruited male participants because of potential gender differences in cooperative behavior (De Dreu and Kret, 2016; Kummerli et al., 2007). The sample size was determined based on previous rTMS studies about cooperation and social decision-making (Bardi et al., 2017; Baumgartner et al., 2013; Krall et al., 2016; Ortiz-Tudela et al., 2018). Three participants were excluded from the analyses during data collection (see Supplementary Methods for details). Thus, data obtained from 22 participants were analyzed (aged 21–32 years, mean  $\pm$  SD = 26.5  $\pm$  3.9 years). All participants were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). No participants met the criteria for any psychiatric disorders, according to evaluation by an experienced psychiatrist using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I). No participants had a history of head trauma, serious medical or surgical illness, or substance abuse. Participant IQ was estimated as 104.2  $\pm$  8.5 using a Japanese Version of the National Adult Reading Test short form (Matsuoka et al., 2006).

Participants' individual differences in dispositional empathy were assessed using the 28-item Interpersonal Reactivity Index (IRI), which is one of the most widely used self-report measures of empathic personality traits (Davis, 1985; Fujino et al., 2014a; Sakurai, 1988; Shamay-Tsoory et al., 2009). Based on previous studies (e.g., Gong et al., 2017; Seidel et al., 2012), the sum score of the IRI was used to assess the association with the cooperation ratio in the MSG task. Furthermore, altruistic disposition was evaluated using a 20-item altruism scale (Nakao et al., 2011; Rushton et al., 1981). Higher scores on these measures were associated with more empathic and altruistic dispositions, respectively.

This study was approved by the institutional review board of Showa University Karasuyama Hospital and was conducted in accordance with the Code of Ethics of the World Medical Association. After all the participants received a complete study description and written informed consent was obtained from each person.

### 2.2. Study design and rTMS

Participants attended two experimental sessions where they received rTMS [either real (cTBS) or sham rTMS] before engaging in the MSG task. The experimental sessions were separated by at least 1 week to prevent a carryover effect, as reported previously (de Jesus et al., 2014). In addition, to control for order effects, the order of application of the stimulation condition in each session (cTBS or sham rTMS) was counterbalanced between the participants, based on prior studies (Krall et al., 2016). Further details are provided in Supplementary Methods.

An inhibitory rTMS protocol (cTBS) was applied for the actual rTMS (Huang et al., 2005). Bursts of three stimuli at 50 Hz were repeated with a frequency of 5 Hz for 40 s, resulting in a total of 600 pulses (Krall et al., 2016); the stimulation intensity was set to 80% of the active motor threshold (Fujino et al., 2020, 2021). For the sham rTMS, we implemented the same stimulation parameters used for the cTBS (location and rTMS pulse properties) using a sham coil (Magstim Company). Before the experiment, structural T1-weighted magnetic resonance imaging

scans of each participant were obtained on a 3 T Siemens Verio scanner with a 12-channel phased-array head coil. Three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequences (TE = 3.06 ms, TR = 2000 ms, TI = 990 ms, FOV = 256 × 256 mm, matrix = 256 × 256, resolution = 1.0 × 1.0 × 1.0 mm<sup>3</sup>, and 208 total axial sections without intersection gaps) were used. The right TPJ was localized at the Montreal Neurological Institute coordinates obtained in a previous meta-analysis study (Mars et al., 2012). We used the coordinates of the posterior part of the right TPJ (x = 54, y = -55, z = 26), which was reported to play a crucial role in social cognition (Mars et al., 2012; Singer and Lamm, 2009). The right TPJ coordinates were transformed into the native space of each participant's scan using BrainVoyager QX TMS Neuronavigator software (Brain Innovation, Maastricht, Netherlands). A Zebris CMS20 ultrasound-based system (Zebris Medical GmbH, Isny, Germany) was used for head and coil registration and monitoring.

The cTBS was expected to disrupt activity in the stimulated brain region for at least 25–45 min (Huang et al., 2005; Krall et al., 2016). Because all participants completed the MSG task approximately 15 min after the stimulation, it was expected that the applied rTMS protocol would reduce the excitability of the stimulated region for the duration of task performance. For further details, see Supplementary Methods.

### 2.3. Priority game task (modified snowdrift game: MSG)

Participants engaged in a series of iterated MSG task (modified cross-traffic intersection version: Qi et al., 2015; see Supplementary Methods).

Participants were instructed to play the role of the driver in one of two cars trying to cross the intersection at the same time (Fig. 1). Participants made decisions on whether to stop (cooperate) or not stop (defect) multiple times. If they stopped, participants (and opponents) were able to cross the intersection and avoid accidents, which was a gain shared with the opponent driver. If they did not stop, participants might cross the intersection more quickly, but they risked accidents that prevented safe passage. To study how an explicit grasp of situational context could influence a participant's cooperative decision, additional social cue conditions were added (i.e., with and without figures showing elderly and pregnant passengers in the game opponent's car; Fig. 1).

As a cover story, participants were instructed that they would play online with anonymous partners who were unfamiliar to them and were present in another room. In reality, these partners were not real people, and the participants played against a computer that was programmed in advance. Each participant played 48 rounds under two conditions (with and without the explicit social cue, 24 rounds each), and the fictional initial of the name for the opponent was displayed before each

condition. The responses of the opponent in two conditions (cooperate or defect) were predetermined and were displayed in pseudo-random order. Specifically, the opponent player cooperated for one-half of the rounds (thus, cooperated and defected for 12 rounds each, under each of the two respective conditions).

Moreover, we created two versions of the MSG task (versions A and B) to examine the effects of the stimulation condition (cTBS vs. sham rTMS) on the behavioral data. These two versions were identical except for the order of the two conditions within the MSG task (i.e., explicit social cue condition first or no explicit social cue condition first), and the fictional initial of the names for the opponent players and the order of their responses (cooperate or defect). All participants performed both versions of the task, and the order of the versions was counterbalanced across participants. At the end of the last session, for confirming whether the MSG task was well understood, the participants had a post-experiment interview regarding the strategies they used, based on previous studies (Fujino et al., 2017; Tei et al., 2018, 2019a). This experiment was conducted using E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA, USA).

Each of the trials was rewarded with points that depended on both players' choices. There were four possible outcomes: player A (participant) and player B (opponent) cooperate (CC), player A cooperates and player B defects (CD), player A defects and player B cooperates (DC), or both players A and B defect (DD). The payoffs for the outcomes were determined as DC > CC > CD > DD (Nowak and Sigmund, 2004; Qi et al., 2015). Each cell of the payoff matrix corresponded to one of these four outcomes (Fig. 2). The experimental instructions of the MSG task are stated in the Supplementary Methods (Appendix 1). Finally, in this MSG task, we defined cooperation ratio as the number of rounds in which the participants stopped (i.e., cooperation) divided by the total number of rounds (with and without the explicit social cue, 24 rounds each).

### 2.4. Statistical analysis

Data were analyzed using SPSS, version 26 (IBM Corp., Armonk, NY). Statistical significance was set at  $p < 0.05$  (two-tailed). First, for the cooperation ratio of the MSG task, we performed a repeated analysis of variance (ANOVA) for examining the effect of stimulation (sham vs. cTBS), the effects of condition (no-cue vs. with-cue), and the interaction of these factors. Second, we examined the association between the cooperation ratio of the MSG and prosocial (empathic and altruistic) traits after log transformation. The analyses were performed after controlling for age because prosocial traits and cooperation have been shown to be associated with age (Schieman and Gundy, 2000; Sun et al., 2018). Finally, we assessed the statistical difference of these correlation

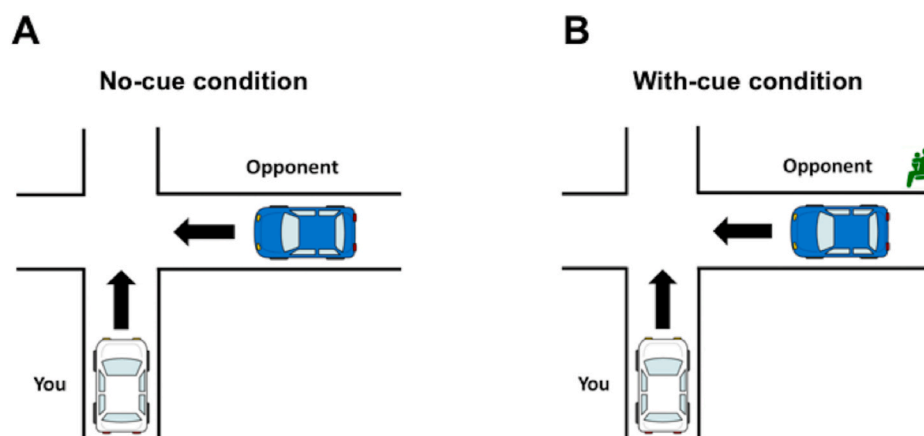
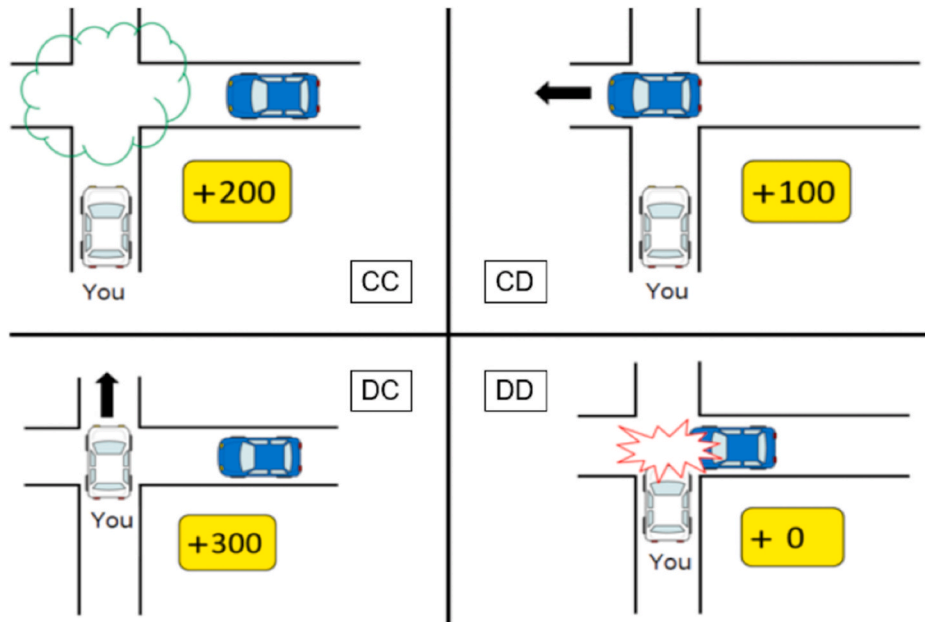


Fig. 1. An illustration of the cross-a-crossing version of the snowdrift game. The current modified snowdrift game (MSG) task included two conditions with or without figures showing elderly and pregnant passengers in the game opponent's car: (A) describes the no-cue condition and (B) with-cue condition.



**Fig. 2.** Payoff matrix of the participants in the MSG task. Four values (in yellow highlights) in each cell correspond to the payoff points to the participants (described as “you” in the figure). Four labels (in alphabet) in each cell correspond to the choice outcomes: player A (participants in the white car) and player B (opponents in the blue car) cooperate (CC), player A cooperates and player B defects (CD), player A defects and player B cooperates (DC), or both player A and player B defect (DD).

coefficients between stimuli conditions based on the previous studies (Arriaga et al., 2019; Fujino et al., 2016; Steiger, 1980).

### 3. Results

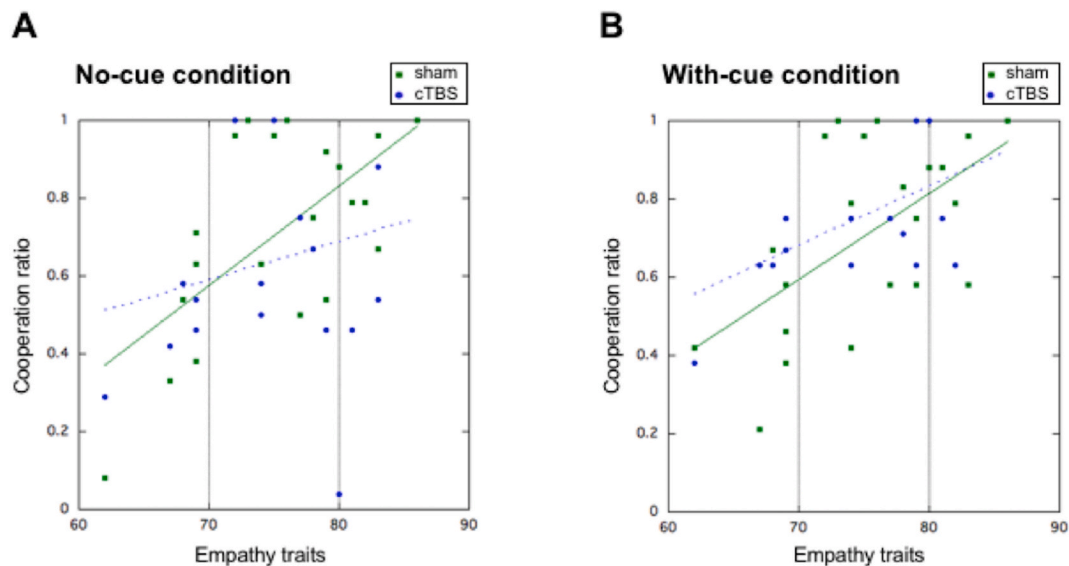
#### 3.1. Cooperation ratio after sham stimulation and cTBS

The results of ANOVA showed that the main effect of the stimulation was not significant ( $F = 0.17, p = 0.68$ ), implying the absence of statistical difference in the overall cooperation ratio between the sham stimulation and cTBS. Moreover, the main effect of condition ( $F = 0.19, p = 0.67$ ), and the condition  $\times$  stimulation interactions were

nonsignificant ( $F = 0.13, p = 0.72$ ). The details of the cooperation ratio are summarized in the Supplementary Materials (Figs. S1–S3 and Table S3). In addition, on the basis of previous rTMS studies (Kuhnke et al., 2020), we performed a complementary Bayesian analysis (Lakens et al., 2020; Wagenmakers et al., 2018). The analysis corroborated the statistical absence of the rTMS effect on the cooperation ratio in the no-cue and with-cue conditions (please see the Supplementary Results for details).

#### 3.2. Associations between the cooperation ratio and prosocial traits

We investigated the association between a participant’s cooperation



**Fig. 3.** Scatter plot of scores on the empathic trait and cooperation ratio in the MSG task after sham stimulation and cTBS under the (A) no-cue and (B) with-cue conditions. After sham stimuli, there were statistically significant positive associations between empathic trait scores and the cooperation ratios under both conditions (with-cue and no-cue conditions). After cTBS, the strength of this association did not reach the statistical threshold in the no-cue condition. In this condition, the difference of correlation coefficients between the empathy trait scores and cooperation ratio after sham/cTBS was statistically significant. For visualization purpose, the figure shows the data without log transformation.

ratio on the MSG task and empathy traits. In the no-cue condition after sham stimuli, the cooperation ratio was positively correlated with empathy trait scores ( $r = 0.70, p < 0.01$ , Fig. 3A). However, after cTBS, the association between the cooperation ratio and empathy score was not statistically significant ( $r = 0.08, p = 0.73$ ). Moreover, the difference in correlation coefficients between cooperation ratio and empathy traits after sham stimulation and cTBS was significant ( $p < 0.01$ ). With the social cue, after both sham stimulation and cTBS, cooperation ratio was positively correlated with empathy trait scores (sham:  $r = 0.61, p < 0.01$ , cTBS:  $r = 0.53, p = 0.01$ , Fig. 3B); and the difference in correlation coefficients between cooperation ratio and empathy traits after sham stimulation and cTBS was not significant ( $p = 0.56$ ). In addition, we examined the association between empathy trait and cooperation ratio changes (i.e., the gap in their cooperation ratio obtained by subtracting the cooperation ratio during cTBS from that during sham). The change in the cooperation ratio between active and sham (i.e., sham minus cTBS) significantly correlated with their empathy measure during the no-cue condition ( $r = 0.43, p = 0.045$ ), but it was nonsignificant during the with-cue condition ( $r = 0.29, p = 0.18$ ).

We also examined the association between the cooperation ratio and scores for altruism traits. In the no-cue condition, after the sham stimulation, cooperation ratio marginally correlated with altruism scores ( $r = 0.43, p = 0.052$ ); whereas, after cTBS, this association was not significant ( $r = 0.27, p = 0.24$ ). With the social cue, after both sham stimulation and cTBS, the cooperation ratio was not significantly associated with altruism scores (sham:  $r = 0.19, p = 0.40$ , cTBS:  $r = 0.31, p = 0.17$ ).

#### 4. Discussion

To the best of our knowledge, this is the first rTMS study to investigate the role of the right TPJ in cooperative dilemmas using the MSG task. Although the cooperation ratio did not statistically differ between the sham stimulation and cTBS, as examined by ANOVA, the strength of association between the cooperation ratio and empathy decreased significantly in the no-cue condition after cTBS. Our results add to our understanding of the right TPJ's function in social cognition, which may be extraordinarily complex. This topic is clearly deserving of further examination.

Contrary to our prediction, the cooperation ratio did not statistically differ between the sham stimulation and cTBS. This may be partly due to the individual variance of our participants (please refer to Figs. S1, S2, S3; Table S3). Several studies have reported considerable intra- and inter-individual differences in responses to rTMS (Davis, 2021; Hinder et al., 2014; Schiller et al., 2014). Moreover, cTBS can result in a disruption of the activity of the target brain region in most participants, while this stimulation may enhance its activity in other participants (Blumenfeld et al., 2014; Hamada et al., 2013; Krall et al., 2016). In this accord, in our MSG task, some participants' cooperation ratio decreased from the sham to cTBS condition, whereas other participants, on the contrary, showed an increase in the cooperation ratio from the sham to cTBS condition. Thus, the absence of a statistically significant difference between the conditions in our task, as assessed by ANOVA, may be a result of large individual differences and/or variation in the strength of task-independent baseline brain activation of our participants. This issue should be further investigated in the future, using both excitatory and inhibitory rTMS protocols.

Intriguingly, the cooperation-empathy link decreased after cTBS in the no-cue condition. After sham stimulation, the empathy trait scores of our participants were positively correlated with the level of cooperation ratio. This is consistent with the growing body of research suggesting that cooperative behavior is associated with empathic personality (de Waal, 2012; Gonzalez-Liencreces et al., 2013). Previous studies have shown that people with greater capacity to consider the perspectives of others or who demonstrate empathic concern are more frequently motivated to cooperate (Rumble et al., 2010; De Dreu and Kret, 2016).

Notably, after cTBS in the no-cue condition, the strength of the association between empathy and cooperation ratio became insignificant. Furthermore, the change in the cooperation ratio between active and sham (i.e., sham minus cTBS) correlated with their empathy measure during the no-cue condition. These data support the idea that the right TPJ was causally involved in resolving a cooperation dilemma in the no-cue condition in our MSG task. In line with previous fMRI studies (Baumgartner et al., 2012; Declerck et al., 2013; Fukui et al., 2006), our findings support the notion that the right TPJ plays a critical role in spontaneously becoming aware of situations that require cooperation.

In contrast, there were statistically positive cooperation-empathy correlations after cTBS as well as after sham stimulation in the with-cue condition, and there was no significant difference when the correlation coefficients between stimulation conditions (sham vs. cTBS) were compared. This result suggests that cooperative decision processing under with-cue conditions may be less critically reliant on the right TPJ functioning compared with that under the no-cue condition. Previous fMRI studies showed that different neural networks were activated when social and strategic factors were added to the condition in the task related to cooperation (Baumgartner et al., 2015; Bear and Rand, 2016; Spitzer et al., 2007). Considering that the TPJ may serve as a network hub in a hybrid of different levels of cognitive processing pathways (Donaldson et al., 2015; Patel et al., 2019; Tei et al., 2017, 2019b), this brain area may mediate particular social cognitions, such as mentalizing about others' beliefs, cost and benefit consideration, and strategic social choices, by integrating multiple brain network activities (Baumgartner et al., 2012; Fujino et al., 2014b; Gerfo et al., 2019; Hill et al., 2017; Makwana et al., 2015; Tei et al., 2014, 2020). Cooperative decision processing under the with-cue condition may be more critically compensated by other brain regions (e.g., dorsolateral prefrontal areas) in our MSG task compared with that under the no-cue condition. Our findings highlight the state-dependent nature of the right TPJ's function, which is deserving of further investigation in the future.

In addition, further studies are required to extensively illuminate the right TPJ functioning and the associated functional networks (Igelström and Graziano, 2017) as well as to disentangle such complex, cooperation behavior about self and/or other prioritizing besides social cognition in general. Specifically, our results suggesting the TPJ's role in the empathy-cooperation association may further implicate that TPJ is involved in more self/other- and/or general social functions besides cooperativity. In this regard, past studies have shown an inconclusive result on the role of right TPJ functioning. The activation of right TPJ may enhance the representation of self over others during the viewing of their facial images (i.e., prompts self-other discrimination toward self-recognition to facilitate the recognition of oneself; Duffy et al., 2019; Heinisch et al., 2011). Meanwhile, the activation of the right TPJ may also enhance the overcoming of one's self-centered perspective in the visual perspective-taking task and economic game tasks to prompt prosocial decision-making (Soutschek et al., 2016), the spontaneous theory of mind (Bardi et al., 2017), and mentalizing (Hill et al., 2017). In this relation, the right TPJ has also been proposed as a support altruistic behavior that involves situational understanding through empathy (Decety and Lamm, 2006; Tei et al., 2017) and signaling conflicts (moral vs. material values; Obeso et al., 2018).

This study has several limitations. First, although a similar number of participants was recruited in a relevant rTMS study on the right TPJ (Bardi et al., 2017; Baumgartner et al., 2013; Krall et al., 2016; Ortiz-Tudela et al., 2018), our sample of 22 persons is relatively small. Thus, more research with additional participants is needed. Second, the present study recruited only male participants. Given that female participants may cooperate via a different decision strategy and empathic processing (De Dreu and Kret, 2016; Kummerli et al., 2007), the findings here may not be generalized to female participants. A gender effect on cooperative decision-making should be examined in future studies. Third, the results of the MSG task can be affected by the participants' background (e.g., traffic rules in their region and whether they possess a

driving license), and therefore, additional studies examining such factors would be informative. Finally, various dominant strategies have been reported while playing the economic game tasks, and we were not able to consider these aspects (e.g., Pavlov and Tit-for-Tat strategies; Axelrod and Hamilton, 1981; Qi et al., 2015). The effects of such strategies appear somewhat evident in the task response (please see Figs. S1, S2, and S3). It is important to collect the participants' game strategies in an MSG task and implement them in the analyses to further deepen our understanding of TPJ's role. Notwithstanding these limitations, our study extends the understanding of the role of the right TPJ in resolving a dilemma during cooperative decision-making by assessing its different processing of social perceptions. This approach appears to be a promising avenue for investigating social cognition.

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#### Declarations of competing interest

None.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nirp.2021.100033>.

#### Authors' contributions

S.T., J.F., T.I., M.K., R.H., H.T., N.K. and M.N. designed research; S.T., J.F., and M.N. participated in the data acquisition; S.T. and J.F. analyzed data; T.I., Y.Y.A., H.O., M.K., S.S., R.H., H.T., N.K., and M.N. helped with interpretation of data. J.F., S.T., T. I., Y.Y.A., H.O., M.K., S. S., R.H., H.T., N.K., and M.N. wrote the paper. All authors have made intellectual contribution to the work and approved the final version of the manuscript for submission.

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