

## Participation of visual association areas in social processing emerges when rTPJ is inhibited

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### ABSTRACT

During a social evaluation, the right temporo-parietal junction (rTPJ) plays an important role according to its contribution in making inferences about the mental states of others. However, what is the neural response if rTPJ function is inhibited during a mentalizing task? In this study, participants played the Dictator Game with two confederates: one playing cooperation (C) and other playing non-cooperation (NC) role and then they were scanned during a mentalizing test. However, we inhibited rTPJ using transcranial magnetic stimulation (TMS) after they played the game and before they were scanned. In this test, participants read negative (Neg) or positive (Pos) personal situations and then they watched confederate's pictures. Images from the TMS group were compared against controls with no TMS stimulation. After statistical comparison, we found a significantly higher activity in right and left visual association areas (BA 18) during the NCPos > NCNeg condition in the TMS group compared with the No-TMS group. Same visual association areas have been described before when participants are processing visual emotional information or when making a fast social categorization. This could reflect a neural mechanism of socio - emotional categorization that emerges after rTPJ inhibition.

### 1. Introduction

We are highly a social species. This is why our thoughts, emotions and motivations are constantly shape by the way we conceive the social environment around us. In this sense the behavior of others has a deep impact on our acts and also in our social cognitive functions that work behind them. Those cognitive mechanisms allow us to make inferences about intentions and motivations in others in order to set our plan of actions. However, beyond the set of cognitive strategies to meet the social world like reprisal, evaluation or even mentalization, there are other rough ways to obtain information from people.

In cognitive neuroscience the identification of social cues has been broadly investigated through the investigation of mentalization or theory of mind. This is our ability to make attributions about other's mental state [31,40]. This cognitive mechanism motivate social understanding across a variety of context through the consideration of the world from others viewpoint [12]. Although other areas have been related with mentalizing as well like medial prefrontal cortex [6] the

temporo-parietal junction (TPJ) mainly in the right hemisphere (rTPJ), has been consistently found when participants make inferences about other's thoughts [21,40]. This was shown in studies that manifest that the former was related with own's social information and the former with other's social information [23]. In same line, several studies investigating intentions in moral behavior [56], or using false belief tasks [40] or using short theory of mind stories [51] converge saying that this area manifests a consistent activity during other's mind inferences. Also, in a previous work we found that rTPJ was closely related with other's inferences when participants were thinking about feelings of non-cooperators [33], however a comparison with a different rTPJ – inhibited group would allow us to know about brain areas that work along with rTPJ when its activity its temporary blocked. This is, to compare which brain areas are causally modulated by rTPJ.

Talking about rTPJ inhibition, the most common way of modulating its activity is using neuromodulation techniques. Accordingly, transcranial magnetic stimulation (TMS) provides an efficient way to modulate a specific brain region. This technique make use of a coil that

*Abbreviations:* rTPJ, right temporo-parietal junction; TMS, transcranial magnetic stimulation; cTBS, continuous theta burst stimulation; C, cooperation; NC, non-cooperation.

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is placed over the cortex and it produces loops of electromagnetic induction forming a magnetic field that passes through the skull and induces a change in polarization in neural populations [28]. This non-invasive neuromodulation method allows examining possible cause – effect relationship between specific brain activity and interested behavior. If this technique is applied in the context of a mentalizing task, it produces that participants don't consider intentions when moral violations occurs [56] or an interference in the ability to take the others' perspective in faux-pas tasks [11]. However, the impact of TMS effect when inferring mental states in others at this point has been only observed at behavioral level but not in neural level and coupling two methodologies like TMS and fMRI seems promising for this objective.

TMS – fMRI investigations allow to discover how TMS affect brain regions functionality either directly through neural interconnections or indirectly through compensatory mechanisms [27]. Therefore, distant brain functional interactions during cognitive or perceptual task might be revealed when these two techniques are combined [37]. There are a high number of studies combining TMS-fMRI to reveal local or remote brain activations derived from a TMS protocols [2,37,50]. Those have been mainly focused in investigating states of motor system [5], visual attentional [37] and visuospatial abilities [38]. Surprisingly this is the first study to use those methods in a mental process like in mentalizing task. To reveal local or remote brain activation derived from rTPJ inactivation could allow us to understand a more complete neural processing that allow people to make inferences and make judgments about others.

Therefore the objective of this study was to reveal the effect of the absence of rTPJ influence during a perspective-taking task. To this end, we compare new fMRI data collected during a Theory of Mind passive viewing task under the inhibitory effect of a TMS protocol (inhibitory theta burst stimulation) [18] and compare this data with those obtained for Reyes-Aguilar et al. [33]. This is, we replicated the study of Reyes-Aguilar et al. [33] but with the only difference is that we add TMS inhibition of rTPJ. This would allow us to reveal which brain areas are participating along with mentalization network for perspective taking function and that might unmask complementary cognitive mechanisms needed for socialization.

## 2. Material and methods

### 2.1. Experimental rationale

Crucially, the resulting imaging data from this new experiment, allows direct statistical comparison with data collected in Reyes-Aguilar et al. [33] in order to compare well – matched brain images under TMS influence against others without same influence. Readers are referred to review Reyes-Aguilar et al. [33] in order to understand basic methodology used in this experiment. In brief, after participants played the Dictator game (with two confederates) in our laboratory under two contexts of cooperation and no cooperation, they were scanned while watching confederates faces attached to positive or negative personal life situations in last 6 months and imaging how that person should feel in the situation that they just read. This methodology emulates daily life situations where we make inferences of other's mind but a social context has sensitized our perception of he or she. However, an essential difference for our new experiment was that we applied the TMS over rTPJ after participants played the Dictator Game and before participants performed the mentalizing task into the scanner. Under this perspective, rTPJ activity during a socially primed - mentalization task might be affected by TMS and this effect could be clear if we make compare this new data with data obtained with same methodology but without rTPJ inhibition.

### 2.2. Participants

14 male participants between 20 and 30 years old participated in this

study. No Neurological or psychiatric personal antecedent were detected according to persona interview or were detected using the Symptom Check List 90 [13]. Participants were informed about the procedures and partially about the objective of the study and were told that complete objective of the study would be debrief at the en of the study. After participants were informed about confidentiality related with personal data, they signed the informed consent in accordance with the Neurobiology Institute's ethics committee on the Use of Humans as Experimental Subjects.

### 2.3. Social context construction and scanning task session

Construction of cooperative and no cooperative context and material and design of scanning task were constructed exactly as was done in [33]. This methodology has proved to be effective in letting participants being convinced about the cover context of cooperation or no cooperation among players.

A single fMRI scanning run consisted of 68 trials each of which was formed by an emotional situation and a picture of the confederate or stranger (although trials with strangers were not included for statistical analysis on this experiment). A figure of the trials and time for each of the screens during the trial can be found in [33]. For the present experiment participants only watched two fMRI runs lasting 9.5 min each. This was done because of the TMS effects will start washing. Since following TMS, participants came back to the scanner and the procedure of localization and calibration needed to be completed for the fMRI scanning session and the last 2 runs could be out of the range of the effect produced by TMS. Stimuli during the fMRI were presented on a black background via PsychoPy [29] and MR compatible button system and goggles (NordicNeuroLab, Bergen, Norway) were used as a synchronized projection system.

### 2.4. Transcranial magnetic stimulation session

As soon as participants finished the Dictator Game they were taken to the Resonance Magnetic Unit in order to perform the MR scanning and TMS sessions. First, a high-resolution structural 3D-T1-weighted images covering the whole brain were acquired for anatomical localization (resolution of  $1 \times 1 \times 1 \text{ mm}^3$ , TR = 2.3 s, TE = 3 ms), and transferred to the analysis workstation, used to perform the coordinate-based neuro-navigation guided TMS session in a neighboring room to the scanner. For each participant, structural images were processed using the Brain-Voyager TMS Neuronavigation module and the stereotaxic process was performed using the digitizer hardware (BrainInnovation, Maastricht, The Netherlands). The high-resolution anatomical scanning was used for anatomical reconstruction of the whole neocortex for each participant. The surface reconstruction was done first through the inhomogeneity correction of signal intensity and then performing a segmentation of white-matter boundaries using a region growing method. Using this structural brain model the TMS ROI was set in the right temporo-parietal junction. This was done according to coordinates obtained from Saxe and Wexler [40] in MNI coordinates ( $x = 54, y = -54, z = 24$ ) at the peak coordinates related with mentalizing function. This step-by-step coregistration procedure has been described before [10].

We used an inhibitory protocol to minimize rTPJ functional activity, 3-pulse burst at 50 Hz were delivered every 200 ms for 40 s. The name of this repetitive TMS protocol has been defined as continuous theta burst stimulation or cTBS [18]. It has been demonstrated that the effect of this protocol last around 45–60 min [46].

### 2.5. Procedure of the scanning task

After participants finished the Dictator Game, and the structural MR imaging was acquired, and the neuronavigated TMS was performed. On the rTPJ, participants came back to the scanner room in order to perform 2 fMRI runs of the stimuli task. Participants were instructed to press a

button in order to ensure that the participants read all the text in the allotted time. After participants finished the scanning sessions, they were explained about the objective of the study.

### 2.6. Image acquisition

All MR images were acquired in a 3.0 T GE MR750 scanner (General Electric, Waukesha, WI, USA). We used a 32-channels head coil to obtain 38 functional images using a T2\*-weighted EPI sequence with TR/TE 2000/40 ms, field of view of 25.6 cm, a 64 × 64 matrix and 4-mm slice thickness, resulting in a 4 × 4 × 4 mm<sup>3</sup> isometric voxel.

### 2.7. fMRI data analysis

Image analysis was performed using FSL 5 (FMRIB's Software Library<sup>2</sup>) [57]. For the statistical analysis we used the FMRI Expert Analysis Tool using FMRIB's Improved Linear Model (FEAT FILM) Version 5.98. Motion and slice timing correction was performed for each participant data and was normalized onto MNI brain common space (Montreal Neurological Institute, EPI Template, voxel size 2 × 2 × 2 mm<sup>3</sup>). We also smoothed functional data from each participant using a Gaussian filter (full width half maximum = 6 mm) and high-pass filtered during analysis. We instructed participants to imagine how that person should feel in emotional situations and the blood oxygen level dependent (BOLD) signal we obtained during the facial pictures presentation. This was done since participants were instructed to imagine, during face presentation, how that person should feel in the previously read emotional situations. We carried out the statistical analysis of the event-related hemodynamic changes using the general lineal model (GLM). The model included four regressors: CPos, CNeg, NCPos and NCNeg. The first level and the fix-effects model were performed in the same way as in Reyes-Aguilar et al. [33] in order to make compatible the two groups of study. The threshold for cluster significance for the first-level was set in Z > 2.3 with p < 0.05 corrected for multiple comparisons with Gaussian Random Field (GRF) for results at the whole-brain level [54]. However we did not performed the group-level analysis. Instead we made a t-test with the objective of compare fMRI images from 14 male participants from Reyes-Aguilar et al. [33] with fMRI data of 14 male participants under the effect of an inhibitory cTBS protocol. For the final analysis, we included only images from the first two runs of data from the first experiment since we performed only two runs in our experiment.

## 3. Results

Among all conditions, we only found one significant comparison between the two groups (see Table 1). We also found higher activity in the visual association region for the TMS group compared with the no-TMS group only during the NCPos > NCNeg. Fig. 1 manifests different slices of significant results in visual association region.

## 4. Discussion

Using previous fMRI data compared with ours we revealed that if we inhibit rTPJ activity, the visual association areas presented a significant effect during a perspective-taking task. This result was surprisingly for us since we were expecting a significant lower activity in the rTPJ in the TMS group compared with no-TMS group during a perspective taking tasks. However, the significant finding was localized in a remote brain area from mentalizing network as in the BA 18. Although has been

shown that TMS interrupt the processing of information that flows into a specific net [47], our results did no show a specific effect over mentalizing network. This is in line with Ruff, Driver & Bestmann [37] assumption that explain how TMS-fMRI technique can reveal the different functional contribution of distant brain region that is not anatomically related with stimulated area [35,37]. According to these authors, the TMS effect over a specific network is not context - independent and fMRI findings under TMS effect might depend on the way a specific network is working. For example, Bestmann et al., [5], found that TMS stimulation over premotor areas affected in a different manner the same area in the opposite hemisphere according to if participants were on resting or active (motor task) condition. These differences were also dependent on the intensity of the stimulation. Result in same line were found by Ruff et al., [36] when TMS over right (but not left) frontal areas increase activity in V1-V4 regions when visual stimuli were absent but decrease the activity in V5 regions when stimuli were present. According to these notions, perhaps the lack of significant results in mentalizing network during a perspective - taking task between the two groups was because this network was active while participants were imagine how non-cooperators felt while passing through a positive experience and this opened the door to the manifestation of the activity in visual association areas. Perhaps these areas have an important role during the mentalizing ability and this potential role is explained next.

At neural level, an explanation for visual association activation might be related with an enhancing attention mechanism according to the emotional salience of the socio - emotional stimuli. In the one hand, it has been shown repeatedly that occipital areas like those that we found as significant, has been related with emotional information processing [19,25,26,43,44] and more specifically with negative valence information [42] likewise when people deceive others during a money distribution [52]. On the other hand, same areas have been shown as active when participants listening to socially salient information as angry related stimuli compared with neutral sounds [39] or when avatars engage in social interaction with participants compared when avatar doesn't [41], or when processing highly socially provocative aggression [22]. Using a different technique, it has been demonstrated that medial visual association areas has a dependent activity with nicotine and perhaps this correlation manifest improved attentional performance in response to task related cues [15]. Therefore, it sounds plausible that socio - emotional information as when processing non-cooperation plus positive information, is allowing an enhancement of visual - emotional areas that increase its activity when a salient and socio - negative information is processing. Maybe this is part of our neural activity of anger when see that a foe is receiving benefits from life. But the interpretation of this finding might goes beyond the attentional enhancement for social stimuli. rTPJ has been related with detection of salient information as a bottom - up mechanism for detecting relevant information [9,55] and its blockage might be highlighting the activity on an area that is commonly activated by the dorsal frontoparietal network as the visual area [58]. This would be in line with the proposal that inferior parietal regions has been shown as related with the awareness of salient visual information [53].

Another line of discussion is related with the priming effect that is derived from playing the dictator game. The awareness of socio - emotional stimuli from dictator game is perhaps signaling the visual association areas and therefore sensitizing this area for processing non-cooperation plus positive condition during scanning session. This is perhaps according to its functional connectivity with subcortical structures like amygdala [3] or from cingulate cortex [8]. This is line with the conceptualization of the emotional prime model that mention that

**Table 1**

TMS: group that receive TMS stimulation; NoTMS: group that did not receive TMS stimulation; NCPos: NoCooperation and positive condition.

|                   | Hemisphere | Anatomical region        | BA | x | y   | z  | p     | k   | z   |
|-------------------|------------|--------------------------|----|---|-----|----|-------|-----|-----|
| TMS > NoTMS NCPos | L / R      | Visual association areas | 18 | 4 | -86 | 22 | 0.043 | 771 | 3.2 |

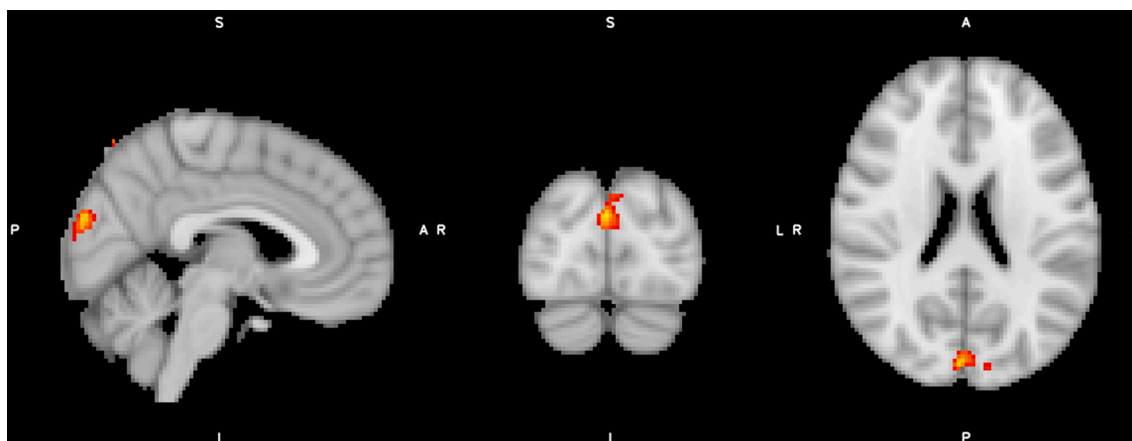


Fig. 1. Significant brain areas when rTPJ is inhibited and contrasted against a NoTMS group.

sensory encoding of affective social cues might work as a primer to engage associations, representations and action programs that derives to appetitive or aversive motivational systems [24]. In other words, visual association areas would allow to information related with past experiences to keep present in order to use it to modify appetitive or aversive systems [25]. A behavioral manifestation of this issue, is when a previous negative affective state in the observer influence posterior judgment about another person trait behavior [17]. At neural level, it was shown that visual occipital system strongly activates in a participant's affective engagement elicited by emotionally salient cues in order to facilitate the posterior sensory encoding of affective stimuli [59,60]. According to our site of stimulation, this interpretation would mean that occipital areas might causally work as a primer area that work together with mentalizing network in order to make a complete interpretation of other's mind. Whether this parallel occipital function represents a complementing (in conjunction) mechanism or a supporting (independently) mechanism for mentalizing network, is still subject of research. A line for investigation derived from these observations could be related with how we are sensitized by socio – emotional information that affect our mentalization skills.

Another function that might be revealed by our occipital significant activation that could fit with previous explanation could be related with categorization. Categorization is the process by which discriminably different things are classified into groups and are thereby rendered as equivalent [61] without an elaborated social strategy [4]. This is a coarse perceptual function that is parallel to a full and detail encoding of stimuli [1]. In the study of categorization, there are some reports that have related medial occipital activity when making the discrimination between in-group – out-groups differences [14], when participants are asked to classify pictures according to different categories like personal identity or work occupation [49], when participants need to discriminate stimuli according to gender, race and color of the picture [45] or when participants watch candidates from opposite political party [20]. This is also in same line with a study that related superior occipital areas with social stereotyping [32]. This ability to make stimuli classifications in occipital regions might be bound together by another function manifested in this area like semantic classification as has been demonstrated by studies that ask participants to establish associations between different stimuli like Latin letters, geometrical figures, and Korean letters [30] or when comparing animals and objects semantic classification against just perceiving them [48]. Perhaps the emotional processing related with this area, explained above, play along with its semantic categorization function to allow fast and rough categorization that assists mentalizing network to facilitate the sensitivity processing of same stimulus when is presented again. Whether our functional images were reflecting the social context (non-cooperation) or the emotional valence (Positive) information, would be a further scope of analysis maybe using

a multivariate approach in order to establish a strong connection between each condition and a particular brain region. This categorization function potentially related with mentalizing abilities might explain some pattern of behavior as when we categorize as foes a specific population without considering mental states (xenophobia) or when we categorize as friends a group of people without considering other's intentions in our mental personal analysis (ravening wolves with sheep's clothing).

A possible benefit for clinical practice of these findings is based on the alteration in the activity of the cuneus and the effects on social behavior that different types of patients present, such as cannabis users or patients with depression. For example, cannabis-users patients showed lower and higher activity, in the right and left cuneus respectively, compared to non-users, while participants thought about how the characters of some representative figures that interacted with co-operators and non-cooperators felt [34].

Likewise, in another group of patients, such as people with depression with a history of child abuse, a positive correlation was found between scores of traumatic experiences in childhood with an activity in cuneal regions while the participants took the perspective of some characters in a cartoon. That involved social interaction [16]. This finding may coincide with what Brooks and Freeman [7] which state that higher order social cognitive processes can be seamlessly integrated into visual perceptual processing, fundamentally shaping social perception. From this perspective, these data could help us to recognize associative mechanisms that allow an integration of functions that give rise to behavior as complex as social behavior and opens a possibility for potential treatments for people with impairments in social behavior, such as through of the use of transcranial magnetic stimulation to promote social behavior through the modulation of the activity of this region.

## 5. Conclusions

According to our findings, we think that TMS – fMRI technique is effective for revealing areas that are working behind scene in any information processing, in our case in the mentalizing function. Also, visual association areas activity might be providing some features that are important for mentalization processing like social, saliency and negative information. Finally, visual association areas might be primed by awareness from socio-emotional stimuli and this is cognitively allowing a social categorization and perhaps also influencing mentalization process. We think that a limitation of the present study is that we did not applied TMS over a control site. This would strengthen our results related with rTPJ activity. Another limitation is that we cannot assure which condition (cooperation, non-cooperation, positive, negative) is specifically related with the visual association areas.

## Author contributions

JCH-O, AR-A and FAB developed the study concept, contributed to the study design. JCH-O and EHP ran the experiment. Data administration and MRI work LG-S and EHP. Data analysis and interpretation was performed by JCH-O, AR-A and FAB. JCH-O, AR-A wrote the manuscript draft, and prepared the figure. All work was done under the supervision of FAB, and all authors provided critical revisions and approved the final version of the manuscript.

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