BRAIN RESEARCH ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Brain Research

Research Report

The effect of rTMS over the inferior parietal lobule on EEG sensorimotor reactivity differs according to self-reported traits of autism in typically developing individuals ☆

Ignazio Puzzo[a,b,*], *Nicholas R. Cooper*[b], *Simona Cantarella*[a,b], *Paul B. Fitzgerald*[c], *Riccardo Russo*[b]

[a]*Centre for Integrative Neuroscience and Neurodynamics, University of Reading, Whiteknights Campus (Earley Gate), Reading RG6 6AH, United Kingdom*

[b]*Centre for Brain Science, Department of Psychology, University of Essex, Wivenhoe Park, Colchester CO4 3SQ, United Kingdom*

[c]*Monash Alfred Psychiatry Research Centre, The Alfred and Central Clinical School, Monash University, Melbourne, Australia*

ARTICLE INFO

Article history:
Accepted 10 October 2013

Keywords:
EEG/repetitive TMS
Human Mirror Neuron System
Traits of Autism in the normal population
Sensorimotor reactivity

ABSTRACT

Previous research suggested that EEG markers of mirror neuron system activation may differ, in the normal population as a function of different levels of the autistic spectrum quotient; (AQ). The present study aimed at modulating the EEG sensorimotor reactivity induced by hand movement observation by means of repetitive transcranial magnetic stimulation (rTMS) applied to the inferior parietal lobule. We examined how the resulting rTMS modulation differed in relation to the self-reported autistic traits in the typically developing population. Results showed that during sham stimulation, all participants had significantly greater sensorimotor alpha reactivity (motor cortex—C electrodes) when observing hand movements compared to static hands. This sensorimotor alpha reactivity difference was reduced during active rTMS stimulation. Results also revealed that in the average AQ group at sham there was a significant increase in low beta during hand movement than static hand observation (pre-motor areas—FC electrodes) and that (like alpha over the C electrodes) this difference is abolished when active rTMS is delivered. Participants with high AQ scores showed no significant difference in low beta sensorimotor reactivity between active and sham rTMS during static hand or hand movement observation. These findings suggest that unlike sham, active rTMS over the IPL modulates the oscillatory activity of the low beta frequency of a distal area, namely the anterior sector of the sensorimotor cortex, when participants observe videos of static hand. Importantly, this modulation differs according to the degree of self-reported traits of autism in a typically developing population.

☆System Neuroscience and Behaviour.

*Corresponding author at: Centre for Integrative Neuroscience and Neurodynamics, University of Reading, Whiteknights Campus (Earley Gate), Reading RG6 6AH, United-Kingdom. Fax: +44 118 378 6715.
E-mail addresses: I.Puzzo@reading.ac.uk, ignaziopzz@gmail.com (I. Puzzo).

0006-8993/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.brainres.2013.10.016

1. Introduction

The electroencephalographic (EEG) sensorimotor mu rhythm is composed of two main frequency components: the alpha component (8–12 Hz) and the low beta component (12–20 Hz). At rest, these components show a synchronised activity, leading to high-amplitude alpha and low beta oscillations. This synchronised activity is abolished during movement and significantly reduced during observation of movement, therefore indicating activation of the primary motor cortex (Hari, 2002, 2006). In line with these findings, EEG and MEG studies demonstrate that desynchronization of sensorimotor rhythms occurs not only during action execution (Gastaut and Bert, 1954; Chatrian et al., 1959; Pfurtscheller and Aranibar, 1979; Semlitsch et al., 1986), but also during action observation (Babiloni et al., 2002; Cochin, Barthelemy, Lejeune, Roux, & Martineau, 1998; Cochin et al., 1999; Muthukumaraswamy and Johnson, 2004; Perry & Bentin, 2009; Pineda, 2005; Streltsova, Berchio, Gallese, & Umilta', 2010). Most studies concentrated on a specific alpha range rhythm (8–12 Hz). However, a number of studies have demonstrated the multispectral nature of the sensorimotor mu rhythm (Avanzini et al., 2012; Hari, 2006; Puzzo et al. 2011; Puzzo et al., 2010; Tiihonen et al., 1989). Therefore, in the present study we investigated the reactivity of two sensorimotor frequency bands: alpha (8–12) and low beta (12–20). Together with the EEG and MEG studies mentioned above, a considerable number of brain imaging studies have reported that a parietal–frontal circuitry is activated both during action execution and action observation (Arnstein et al., 2011; Caspers et al., 2010; Molenberghs et al., 2012). In agreement, TMS studies have shown that observation of motor acts modulates the activity (increase in size of motor evoked potentials) in the muscles involved with the execution of the same motor acts (Fadiga et al., 1995; Gangitano et al., 2001).

These findings have been interpreted in the framework of mirror neurons. Mirror neurons are a specific family of neurons located in area F5 of the macaque monkey premotor cortex and inferior parietal lobule (IPL) that fire both when the macaque performs an action and when it observes another individual (macaque or human) performing the same action (Di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Fogassi et al., 2005; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). It is argued that the main functional role of parieto-frontal mirror neurons of macaque monkeys is to automatically understand motor acts performed by others by matching them to the their own motor repertoire (Rizzolatti et al., 2001).

Various cognitive neuroscience methods including functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS), and EEG have provided indirect evidence of the existence of an observation–execution matching system in human beings (often referred to as the human mirror neuron system or hMNS). This system allows perceived actions to be directly matched with their corresponding representations within an observer's own motor repertoire (see Rizzolatti and Craighero, 2004 for a review). Changes in EEG power in the mu frequency components over sensorimotor areas during action execution or action observation have been suggested to reflect a downstream modulation of these areas by mirror neurons in the premotor cortex; hence mu activity can be considered to be an EEG marker of the hMNS activity (Pineda, 2005). Recently, Arnstein et al. (2011) provided evidence that mu desynchronisation during action execution and action observation is a valid index of the hMNS. They showed that mu desynchronisation covaried with Blood-oxygen-level dependence (BOLD) response in hMNS areas including inferior parietal lobe (IPL), dorsal premotor (dPM) and primary somatosensory cortex (BA2) during action execution and action observation.

It is argued that during movement observation, the human mirror neurons located in the inferior parietal lobule (IPL) and in the inferior frontal gyrus (IFG) are activated and this activation modulates (via cortico-cortical connections) the activity of the sensorimotor areas which most likely simulate the movement observed (Rizzolatti and Craighero, 2004). Specifically, it is suggested that during biological movement observation, the superior temporal sulcus (STS) provides a higher-order visual description of the action to be simulated, whereas the parietal component (IPL) of the hMNS would be concerned with the motoric aspects of the observed action and the frontal (IFG) component of the hMNS would be concerned with mapping the observed action into the observer's motor repertoire.

It is suggested that such a sensorimotor simulation mediates the recognition and understanding of actions observed by humans (Iacoboni and Dapretto, 2006).

1.1. *Autism and the hMNS*

Part of the symptoms that characterise autism spectrum disorders include impairments in communication, imitation and emotion as well as the ability to understand others' intentions. These deficits seem to match the functions attributed to the hMNS. Evidence of a dysfunctional hMNS in individuals with autism spectrum disorder (ASD) that could constitute the underlying neural substrate of the social cognition deficits evident in this clinical population is still under debate. Some research groups have shown a lack of mirror neuron system activation in ASD individuals compared to controls (e.g., Oberman et al., 2005; Bernier et al., 2007) and others have a contrary view (e.g., Southgate et al., 2008); Raymaekers et al., 2009). Research in our lab showed differences in EEG (low beta event – related desynchronization; ERD) reactivity during hand action versus static hand observation between individuals with high and low traits of autism (measured through the AQ). Specifically, individuals with high traits of autism seemed to activate their anterior sensorimotor cortex no matter whether the video they watched was meaningful hand action or a static hand. Differentially, individuals with low traits of autism seemed to activate the same area significantly more when they saw a meaningful hand action compared to when they saw a static hand. This result suggested a hyperactive modulation of the anterior sensorimotor areas in typically developing individuals with high traits of autism (Puzzo et al., 2010).

Similar results were reported in an fMRI study conducted with high-functioning autistic individuals by Martineau et al., (2010). They found that, unlike typically developing individuals, high-functioning autistic individuals had a bilateral greater activation of inferior frontal gyrus during observation of human hand motion compared to human static hand observation. Therefore, they concluded that this hyperactivation of the

Please cite this article as: Puzzo, I., et al., The effect of rTMS over the inferior parietal lobule on EEG sensorimotor reactivity differs according to self-reported traits of autism in typically developing individuals. Brain Research (2013), http://dx.doi.org/10.1016/j.brainres.2013.10.016

inferior frontal gyrus during observation of human motion in autistic individuals provides evidence for the hypothesis of atypical activity of the MNS that may be related to the social deficits in autism (Martineau et al., 2010).

1.1.1. *Modulating sensorimotor reactivity using rTMS*

It has been documented that 10 Hz rTMS delivered over a brain area excites the underlying area (Shah, Weaver, and O'Reardon, 2008). In the context of the current study, we sought to investigate whether rTMS at a frequency based on an individual's peak alpha/mu EEG activity (around 10 HZ) could be used to enhance sensorimotor mirror neuron activity. This was based upon previous research by Klimesch et al. (2003), who showed that rTMS applied at an individually adjusted frequency within the alpha bandwidth plus 1 Hz (i.e., between 8 Hz and 13 Hz and termed "individual alpha frequency" or IAF) not only improved participants' performance on a mental rotation task, but was also accompanied by increased alpha ERD to the task. Over the sensorimotor areas, alpha and low beta suppression are regarded as reflecting activation of the underlying cortex and specifically, during action observation, as indexing activation of the hMNS. Looking at Klimesch's results with IAF+1 Hz rTMS, it seems reasonable that rTMS applied during the period that precedes the task could be used as a tool for influencing the dynamic of the alpha and low beta reactivity, and therefore potentially, hMNS activity.

The principal aim of this study was to investigate the effect of high frequency IAF+1 Hz rTMS delivered to the left inferior parietal lobule, which forms part of the hMNS, on sensorimotor alpha and low beta reactivity during hand movement observation. Furthermore, this study explored whether a hypothesised rTMS influence on alpha and low beta ERD differs according to the extent of an individual's self-reported autistic traits. To address these aims, IAF+1 Hz rTMS was applied to the IPL before stimuli presentation, and the effect of it on EEG oscillatory activity in distant sensorimotor areas was investigated. The IPL was chosen as a target area to be stimulated because previous studies (Decety et al., 1997; Grezes, 1998) using positron emission tomography (PET) have related activity in this area with the observation of meaningless hand actions as opposed to observation of static hands. Therefore the IPL seems to play a role in processing visual properties of hand movement and for generating visuomotor transformations (i.e., direction of the movement in space and kinematics). Because the visual stimuli presented to participants (hand movement and static hand) depicted a right hand, the left inferior parietal lobule (contralateral to the stimuli) was targeted. Alpha and low beta reactivity was assessed by the measurement of event-related desynchronization (ERD) during hand movement observation. ERD is measured as a percentage change of power in the frequency band of interest between the period after the event is given (active period, A; e.g., movement observation) and the period preceding the event (reference period, R; e. g., blank screen; Pfurtscheller and Lopes da Silva, 1999).

Previous research suggests that, unlike individuals with low traits of autism, individuals with high traits of autism show an increased low beta ERD both during hand action and static hand observation (Puzzo et al., 2010). Therefore, in the present study we predict that during sham rTMS the same pattern would be replicated whereas applying active high frequency IAF+1 Hz rTMS over the IPL would have an effect in increasing anterior sensorimotor alpha and low beta ERD during hand movement observation compared to static hand observation and that this effect would be modulated by the degree of self-reported autistic traits. Influencing the sensorimotor alpha and low beta ERD by mean of rTMS would be a crucial finding in that it would inform the creation of a possible clinical intervention for individuals with ASD who have been found to show a lack of sensorimotor alpha reactivity during movement observation.

2. Results

2.1. *Data analysis*

A mixed factorial design was employed for the data analysis. The between subjects factor was "AQ" (individuals with high AQ scores and individuals with average AQ scores). The first within subject factor was "stimulation" (active and sham). The second within subject factor was "hand" (moving hand, static hand) and the third within-subject factor was "electrodes" (FC1, FCZ, FC2). The same data analysis was employed for the C electrodes (C3, C1, CZ, C2 and C4). The dependent variables were the ERD values for the alpha, low beta bands, IAF alpha and IAF low beta IAF bands.

2.2. *FC electrodes (FC1, FCZ, FC2) analysis*

No main effects or interactions were observed in any bandwidth ($Fs < 1$) except the low beta band. A significant interaction between "stimulation", "hand" and "AQ" was found in the low beta band [$F(1, 12) = 8.48$; $p < .05$], (see Fig. 2). Paired-sample t-tests showed that in the sham condition the average AQ group presented significantly greater low beta ERD during moving hand compared to static hand observation [$t(6) = -4.074$; $p < .01$]. No such low beta ERD difference was found for the high AQ group in the sham condition, [$t(6) = 1.784$; $p > .05$]. This differential effect was abolished with active TMS, i.e. no significant differences in terms of low beta ERD were observed in the active TMS condition between static and moving hand observation in either group: average AQ group, [$t(6) = -.07$; $p > .05$] high AQ group [$t(6) = -1.14$; $p > .05$].

Further paired-sample t-tests comparing static hand and moving hand observation between sham and active TMS revealed the following results: The average AQ group participants (see Fig. 2) showed a significantly increased low beta

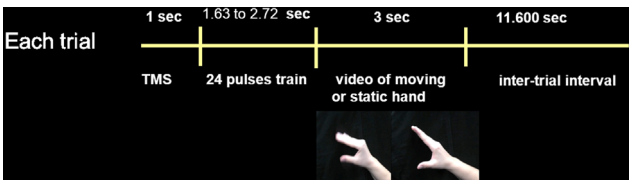

Fig. 1 – Timeline and stimuli of each experimental trial.

Please cite this article as: Puzzo, I., et al., The effect of rTMS over the inferior parietal lobule on EEG sensorimotor reactivity differs according to self-reported traits of autism in typically developing individuals. Brain Research (2013), http://dx.doi.org/10.1016/j.brainres.2013.10.016

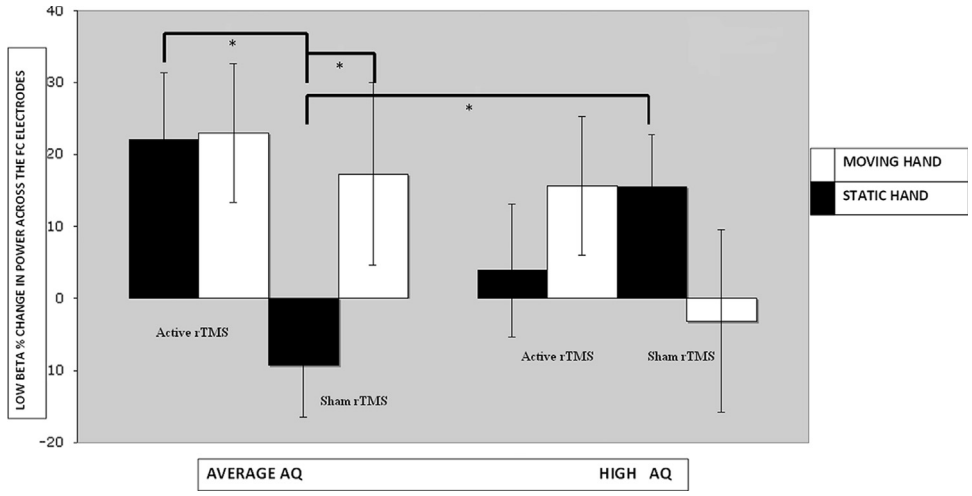

Fig. 2 – Low beta ERD across the FC (FC1, FCZ, FC2) electrodes during hand movement and static hand observation under active and sham high frequency rTMS in the two groups (average and high AQ). Error bars indicate the standard error of the mean. Asterisks (*) denote significant differences.

ERD in the active condition relative to sham condition during observation of the static hand [$t(6)=3.93$; $p<.01$]. No difference in low beta ERD between active and sham conditions during moving hand observation was found [$t(6)=-.90$; $p>.05$]. For the high AQ group, no significant difference in low beta ERD between active and sham TMS during either static hand or moving hand observation was found [$t(6)=-.99$; $p>.05$]; [$t(6)=-1.245$; $p>.05$]. Finally independent samples *t*-tests (2-tailed) compared active and sham rTMS during hand movement and static hand observation between the two groups (average and high AQ). Results revealed that in the sham condition, high AQ individuals had a significantly greater low beta ERD during static hand observation compared to the average AQ individuals [$t(12)=-2.42$; $p<.05$]. No other contrasts were significant.

2.3. *C electrodes (C1, C3, CZ, C2, C4) analysis*

No main effects or interactions were observed in any bandwidth except for the alpha band ($Fs<1$). A significant interaction between the factors "stimulation" and "hand" in the alpha band was observed [$F(1,12)=5.27$; $p<.05$]. Follow up *t*-tests showed that participants during the sham stimulation had significantly greater alpha ERD during moving hand observation than static hand observation [$t(13)=2.63$; $p<.05$]. Whereas, during the active stimulation such a difference in alpha ERD between moving hand and static hand observation was not significant [$t(13)=.762$; $p>.05$] (see Fig. 3). No significant differences between active and sham rTMS were observed when participants watched static hand or moving hand videos [$t(13)=1.80$; $p>.05$]; [$t(13)=1.00$; $p>.05$].

3. Discussion

The aim of this study was to investigate the effect of high frequency rTMS (prior to stimuli observation) delivered to the IPL on sensorimotor alpha and low beta ERD induced by a video presentation of hand movement. The sensorimotor cortex consists of several areas, including: the pre-motor cortex (FC1, FCZ, FC2) and motor cortex (C3, C1, CZ, C2, C4) (Szurhaj et al., 2003). Hence, these were the brain areas systematically explored. The present study also looked at the high frequency rTMS influence on the sensorimotor alpha and low beta ERD in relation to the extent of an individual's self-reported autistic traits.

The general prediction of the present study was that high frequency rTMS relative to sham rTMS applied over the IPL before the stimuli presentation (hand movement versus static hand) would enhance the sensorimotor alpha and low beta ERD during hand movement observation. Results did not support the prediction, in that no significant difference was observed in alpha and low beta ERD between active rTMS stimulation and sham rTMS stimulation over the IPL during hand movement observation in both average and high AQ groups. However, an important unpredicted effect of active relative to sham rTMS was found revealing increased sensorimotor reactivity during static hand observation following active rTMS in the group that had average scores at the AQ.

Beginning with results in the C electrodes, during sham rTMS there was significantly increased alpha ERD while all participants observed a hand movement compared to when they observed a static hand. This EEG sensorimotor reactivity during biological movement has been suggested to reflect a downstream modulation of the parieto-frontal human mirror neuron system during hand movement observation (Rizzolatti and Craighero, 2004). This modulation is suggested to be the result of the hMNS motor simulation of the observed movement. Our results are in accordance with this interpretation. In contrast, during active rTMS there was not any difference in terms of alpha ERD between observing a static hand or a hand movement. Therefore, this result might suggest that participants show a classical sensorimotor reactivity (increased alpha ERD) to hand movement compared to static hand observation when no stimulation (sham condition) is delivered to the IPL. However when active

Please cite this article as: Puzzo, I., et al., The effect of rTMS over the inferior parietal lobule on EEG sensorimotor reactivity differs according to self-reported traits of autism in typically developing individuals. Brain Research (2013), http://dx.doi.org/10.1016/j.brainres.2013.10.016

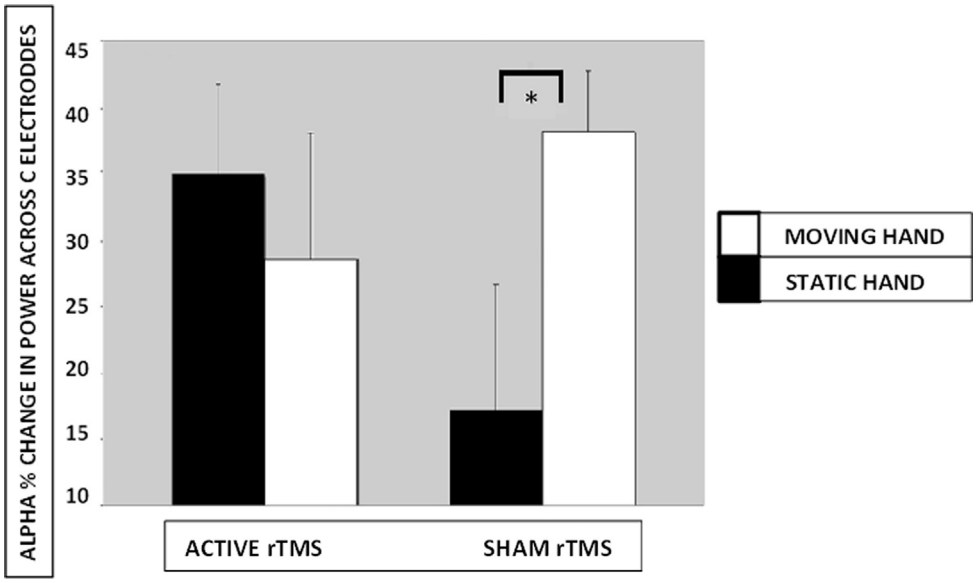

Fig. 3 – Alpha ERD across the C electrodes (C3, C1, CZ, C2 and C4) for both groups combined during hand movement and static hand observation under active and sham high frequency rTMS. Error bars indicate the standard error of the mean. Asterisks (*) denote significant difference.

IAF+1 Hz rTMS is delivered over the IPL, it modulates the reactivity of sensorimotor cortex during static hand observation such that the difference in alpha ERD between hand movement and static hand (observed at sham) is reduced.

Results in the FC electrodes (likely to reflect the activity of the underlying pre-motor cortex: the anterior sector of the sensorimotor cortex) indicated that the average AQ group showed a significant enhanced low beta ERD during hand movement compared to static hand observation in the sham rTMS condition (similar to both groups over the C electrodes). During active rTMS, the average AQ group did not show any low beta ERD difference between the observation of hand movement and static hand. In the average AQ group, when static hand and hand movement observation were compared between sham and active rTMS, it was found that this group showed significantly increased low beta ERD in the active rTMS condition relative to sham condition only during observation of the static hand and not during hand movement observation. This result suggests that in the average AQ group, when no rTMS (sham) is delivered to part of their hMNS (IPL), there is a significantly greater reactivity of the sensorimotor cortex (low beta ERD) during hand movement observation than static hand observation. Conversely, when high frequency rTMS (active) was delivered to the IPL, a significant increase of sensorimotor reactivity (low beta ERD) occurred during static hand observation. This suggests that sensorimotor cortex activation during hand movement observation may not be further enhanced by active high frequency rTMS over the IPL. The high AQ group results indicated no significant differences in low beta ERD between static and hand movement observation either in the sham or in the active rTMS conditions or between sham and active rTMS during static or hand movement observation.

Both results in the C electrodes and FC electrodes showed a similar pattern in terms of the modulatory effect of active rTMS over the IPL on the sensorimotor reactivity. It seemed that active rTMS over the IPL caused an increased reactivity of the sensorimotor cortex only during static hand observation (increased alpha ERD over C electrodes) in all the participants, and that this effect is somehow driven by self-reported autistic trait (increased low beta ERD over FC electrodes). These results suggest that active rTMS over the IPL relative to sham did not modulate EEG sensorimotor activity during hand movement observation. That may be because the EEG sensorimotor reactivity was already at (or close to) its maximum during hand movement observation (although it is likely to be greater during the actual movement execution), arguably due to the fact that the mirror mechanism during hand movement observation was already at work and its performance cannot be further enhanced. However the reported EEG sensorimotor modulation (low beta ERD enhancement) during active rTMS relative to sham registered while participants with average AQ watched static hands videos, suggests that active rTMS over the IPL activated the sensorimotor cortex when this one was under-activated because static hand video observation does not normally trigger sensorimotor simulation (as shown during the sham rTMS session).

Individuals with high traits of autism revealed no significant differences in the anterior sensorimotor low beta ERD between the observation of hand movement and static hand during both active rTMS (over the IPL) and sham rTMS. The fact that active rTMS delivered over the IPL did not have any effect on the anterior sensorimotor low beta ERD could be explained in terms of a general differential way that this portion of the sensorimotor cortex is functioning during hand movement perception in individuals with high traits of autism. Unlike individuals with average AQ, individuals with high autistic traits seem to possess an anterior sensorimotor cortex that reacts similarly to hand movement and static

Please cite this article as: Puzzo, I., et al., The effect of rTMS over the inferior parietal lobule on EEG sensorimotor reactivity differs according to self-reported traits of autism in typically developing individuals. Brain Research (2013), http://dx.doi.org/10.1016/j.brainres.2013.10.016

hand observation and that might be related to a different way in which they perceive biological motion (Puzzo et al., 2010). Thus stimulating the IPL (with active rTMS) in individuals with high traits of autism did not have an effect on the anterior sensorimotor cortex because it might be already hyperactive during both hand movement and static movement observation.

Taking into account the differences between groups (average AQ versus high AQ) it was found that in the sham rTMS, high AQ individuals had a significantly greater low beta ERD during static hand observation compared to the average AQ individuals. Interestingly this latter difference between the two groups replicated previous results from our laboratory (Puzzo et al., 2010) both in terms of frequency band (low beta) and in terms of sensorimotor cortex localisation (FC1, FCZ, FC2: supposedly reflecting the underlying pre-motor areas). This suggests a significant hyperactivation of the anterior sector of the sensorimorotor cortex during static hand observation in individuals with high traits of autism compared to individuals with average traits of autism.

In summary, the present results suggest that during sham rTMS, participants with average AQ scores show increased low beta ERD when they observed hand movement relative to when they observe static hand. This sensorimotor reactivity during movement observation is believed to reflect the activation of the hMNS. During movement observation, the hMNS is activated and this activation modulates (via cortico-cortical connections) the activity of the sensorimotor areas which in turn simulate the movement observed. This mechanism is believed to mediate the recognition and understanding of actions observed by humans (Pineda, 2005; Rizzolatti and Craighero, 2004). We also found that this mechanism could be significantly modulated using individually-adjusted high frequency rTMS (c.10 Hz) but only for the group with average scores at the AQ. Specifically, active rTMS increased low beta ERD to static hand stimuli, thus abolishing the moving-static differentiation described above.

Participants with high AQ during sham rTMS did not show low beta ERD differences between observing hand movement and static hand. In fact, they showed increased low beta ERD during static hand observation in comparison to the average AQ participants. This suggests that in participants with high AQ, the sensorimotor low beta ERD is modulated by the observation of static hand videos and replicates previous findings of a lack of differentiation between moving and still hand observation in high AQ groups (Puzzo et al., 2010).

In summary, our result show that rTMS delivered to the IPL reduced the difference (increased ERD during hand movement compared to static hand observation demonstrated at sham) in sensorimotor alpha (C electrodes) and low beta (FC electrodes) reactivity between hand movement and static hand observation. This reduction seems to be caused by the increase in alpha and low beta ERD during static hand observation when active rTMS was delivered. In conclusion, it is possible to modulate EEG indices of downstream hMNS activation by targeting upstream nodes of the network. Unlike sham rTMS, active rTMS over the IPL modulates the oscillatory activity of the low beta frequency of a distal area, namely the anterior sector of the sensorimotor cortex, when participants observe videos of static hand. Importantly, this modulation differs according to the degree of autism traits in the normal population.

4. Experimental Procedures

4.1. Participants

Fourteen healthy university students (eight males) aged 19–40 (mean age=24.2; S.D.=5.7) participated in the experiment. All were right handed. They were screened in relation to their suitability for TMS using the TASS questionnaire (Keel et al., 2001); other exclusion criteria were any history of psychiatric or neurological illnesses. Participants completed the AQ questionnaire. This served to describe the sample in terms of their autistic traits in order to examine associations between those and hMNS modulation. AQ data collected over two years (247 participants) revealed a general mean score of 16.1 and S.D. of 5.5 (Puzzo et al., 2010; Puzzo et al., 2009). Participants in the present experiment were split in two groups depending on the scores they obtained at the AQ questionnaire. Participants who scored at least 1 S.D. above the general mean formed the high AQ group. Participants who scored within 1 S.D. (within 10.6 and 21.6) formed the average AQ group. This resulted in two groups (High and Average AQ) each containing seven participants. Mean AQ score for the high group was 25.42 (S.D.=5.44) and the mean AQ score for the average group was 16 (S.D.=3.31). Participants gave written informed consent, and received £ 20 remuneration for their participation. The study was granted approval by the University of Essex Ethics Committee.

4.2. Procedure, measures and stimuli

Participants attended two sessions of approximately 60 min each. At the beginning of the first session, the participants' resting motor threshold (RMT) and individual alpha frequency (IAF) were measured: the RMT was measured with the EEG cap on in order to estimate the TMS intensity taking into account the distance between the coil and the scalp. To measure RMT, two electrodes were attached to the participant's right Abductor pollicis-brevis muscle (APB) and a third electrode on their right forearm (ground). A figure-eight coil connected to a Magstim Rapid Trancranial Magnetic Stimulator (Magstim Co. Ltd. UK) was placed over the left primary motor cortex (M1). The intersection of the coil was placed tangentially to the EEG cap with the handle pointing backward and laterally at 45° angle away from the midline. The coil was moved nearby the left motor cortex in order to establish the optimal position from where maximal amplitude of the motor-evoked potentials MEPs was elicited in APB. This procedure allowed us to measure MEPs response to TMS, and thereby determine the individual's RMT defined as the minimal intensity necessary to produce MEPs with amplitude of approximately 50 μV in at least 5 out of 10 trials (Avenanti et al., 2005). Each participant's individual alpha frequency (IAF) was measured to determine the frequency of rTMS. EEG was recorded for 2 min while the participants rested with eyes closed. The IAF was defined as the peak frequency between 8 and 14 Hz during this period recorded from occipital electrodes (O1, OZ and O2),(W Klimesch, 1999).

Participants took part in two separate sessions. In one session they received active IAF+1 Hz rTMS over the IPL (electrode P3 on the EEG cap. See (Herwig et al., 2003; Kim,

Please cite this article as: Puzzo, I., et al., The effect of rTMS over the inferior parietal lobule on EEG sensorimotor reactivity differs according to self-reported traits of autism in typically developing individuals. Brain Research (2013), http://dx.doi.org/10.1016/j.brainres.2013.10.016

2007 for rationale) and in the other session they received sham rTMS (over the same site). The two sessions were spaced at least two days apart. Half of the participants received rTMS in the first session and sham in the second session and the other half vice versa. Each session contained 30 trials (15 moving hands, 15 static hands presented in blocks); and lasted approximately 9 min. Each trial started with the presentation for 1 s. of the word "TMS" followed by a train of 24 pulses with the intensity set at the 110% of the resting motor threshold and the frequency set according to the IAF+1 Hz. Each rTMS train could last from 1.63 s to 2.72 s. depending on the IAF. This was followed by a short video clip of either a still hand or a moving hand shown for 3 s. followed by 11.600 s. inter-stimulus-interval as suggested by (Klimesch et al., 2003), (see Fig. 1). Frequency, duration and number of pulses in each rTMS train, as well, inter-train-interval and rTMS intensity were set according to internationally agreed safety guidelines (Rossi et al., 2009; Wassermann, 1998).

4.3. *EEG recording and analysis*

Electroencephalogram (EEG) was recorded through a 64-channel Synamps2 EEG system (Compumedics, Neuroscan, Texas, USA) and concurrently TMS was delivered over the EEG cap according to previously published methods (Daskalakis et al., 2008; Daskalakis et al., 2008; Fitzgerald et al., 2008).

Eye movements were recorded using four facial electrodes (above and below the left eye and on the outer canthi of the eyes). Impedances for all of the electrodes were reduced to below 10 kΩ before the start of each of the two sessions. Data were continuously sampled at 1000 Hz, with a band-pass filter of .05–100 Hz and a 50-Hz notch filter. Online, EEG data were referenced to a point midway between Cz and CPz and grounded midway between Fz and FPz using the 10–20 electrode positioning system.

Once acquired, data were visually inspected in order to detect and exclude blocks of data that contained the rTMS artifacts. Bad electrodes were also excluded on a participant-by participant basis. Ocular artifact rejection was carried out using linear derivation method (Semlitsch et al., 1986). All data were re-referenced off-line to a common average reference and a second automatic artefact rejection sweep was carried out, with exclusion parameters set at ± 75 mV. The frequencies taken into consideration [sensorimotor alpha (8–12 Hz) and low beta (12–20 Hz] were recorded from the electrodes overlying the sensorimotor cortex pre-central gyrus (FC1, FCZ, FC2) and motor cortex (C3, C1, CZ, C2, C4) as suggested by Szurhaj et al. (2003). ERD was measured as the percentage change in power between the video presentation (test: 500ms to 2547 ms from stimulus on-set) and a reference period (reference: -6000 ms to -4096 ms pre-stimulus onset and pre-rTMS onset) using the following formula: (reference − test/reference) × 100, (Pfurtscheller and Lopes da Silva, 1999).

Funding

This study was supported by a University of Essex studentship to Ignazio Puzzo and a University of Essex Research Promotion Fund grant to Nicholas Cooper.

REFERENCES

Arnstein, D., Cui, F., Keysers, C., Maurits, N.M., Gazzola, V., 2011. μ-suppression during action observation and execution correlates with BOLD in dorsal premotor, inferior parietal, and SI cortices. J. Neurosci. Off. J. Soc. Neurosci. 31 (40), 14243–14249, http://dx.doi.org/10.1523/JNEUROSCI.0963-11.2011.

Avanzini, P., Fabbri-Destro, M., Dalla Volta, R., Daprati, E., Rizzolatti, G., Cantalupo, G., 2012. The dynamics of sensorimotor cortical oscillations during the observation of hand movements: an EEG study. PloS One 7 (5), e37534, http://dx.doi.org/10.1371/journal.pone.0037534.

Avenanti, A., Bueti, D., Galati, G., Aglioti, S.M., 2005. Transcranial magnetic stimulation highlights the sensorimotor side of empathy for pain. Nat. Neurosci. 8 (7), 955–960, http://dx.doi.org/10.1038/nn1481.

Babiloni, C., Babiloni, F., Carducci, F., Cincotti, F., Cocozza, G., Del Percio, C., Moretti, D.V., et al., 2002. Human cortical electroencephalography (EEG) rhythms during the observation of simple aimless movements: a high-resolution EEG study. NeuroImage 17 (2), 559–572 ⟨http://www.ncbi.nlm.nih.gov/pubmed/12377134⟩.

Bernier, R., Dawson, G., Webb, S., Murias, M., 2007. EEG mu rhythm and imitation impairments in individuals with autism spectrum disorder. Brain and Cognit. 64 (3), 228–237, http://dx.doi.org/10.1016/j.bandc.2007.03.004.

Caspers, S., Zilles, K., Laird, A.R., Eickhoff, S.B., 2010. ALE meta-analysis of action observation and imitation in the human brain. NeuroImage 50 (3), 1148–1167, http://dx.doi.org/10.1016/j.neuroimage.2009.12.112.

Chatrian, G.E., Petersen, M.C., Lazarte, J.A., 1959. The blocking of the rolandic wicket rhythm and some central changes related to movement. Electroencephalogr. Clin. Neurophysiol. 11 (3), 497–510 ⟨http://www.ncbi.nlm.nih.gov/pubmed/13663823⟩.

Cochin, S., Barthelemy, C., Lejeune, B., Roux, S., Martineau, J., 1998. Perception of motion and qEEG activity in human adults. Electroencephalogr. Clin. Neurophysiol. 107 (4), 287–295 ⟨http://www.ncbi.nlm.nih.gov/pubmed/9872446⟩.

Cochin, S., Barthelemy, C., Roux, S., Martineau, J., 1999. Observation and execution of movement: similarities demonstrated by quantified electroencephalography. Eur. J. Neurosci. 11 (5), 1839–1842 ⟨http://www.ncbi.nlm.nih.gov/pubmed/10215938⟩.

Daskalakis, Z.J., Farzan, F., Barr, M.S., Maller, J.J., Chen, R., Fitzgerald, P.B., 2008. Long-interval cortical inhibition from the dorsolateral prefrontal cortex: a TMS-EEG study. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 33 (12), 2860–2869, http://dx.doi.org/10.1038/npp.2008.22.

Daskalakis, Z.J., Farzan, F., Barr, M.S., Rusjan, P.M., Favalli, G., Levinson, A.J., Fitzgerald, P.B., 2008. Evaluating the relationship between long interval cortical inhibition, working memory and gamma band activity in the dorsolateral prefrontal cortex. Clin. EEG Neurosci. Off. J. EEG Clin. Neurosci. Soc. (ENCS) 39 (3), 150–155 ⟨http://www.ncbi.nlm.nih.gov/pubmed/18751565⟩.

Decety, J., Grèzes, J., Costes, N., Perani, D., Jeannerod, M., Procyk, E., Grassi, F., et al., 1997. Brain activity during observation of actions. Influence of action content and subject's strategy. Brain J. Neurol. 120, 1763–1777 ⟨http://www.ncbi.nlm.nih.gov/pubmed/9365369⟩.

Di Pellegrino, G., Fadiga, L., Fogassi, L., Gallese, V., Rizzolatti, G., 1992. Understanding motor events: a neurophysiological study. Exp. Brain Res. Exp. Hirnforsch. Exp. Cérébrale 91 (1), 176–180 ⟨http://www.ncbi.nlm.nih.gov/pubmed/1301372⟩.

Fadiga, L., Fogassi, L., Pavesi, G., Rizzolatti, G., 1995. Motor facilitation during action observation: a magnetic stimulation

study. J. Neurophysiol. 73 (6), 2608–2611 ⟨http://www.ncbi.nlm.nih.gov/pubmed/7666169⟩.

Fitzgerald, P.B., Daskalakis, Z.J., Hoy, K., Farzan, F., Upton, D.J., Cooper, N.R., Maller, J.J., 2008. Cortical inhibition in motor and non-motor regions: a combined TMS-EEG study. Clin. EEG Neurosci. Off. J. EEG Clin. Neurosci. Soc. (ENCS) 39 (3), 112–117 ⟨http://www.ncbi.nlm.nih.gov/pubmed/18751559⟩.

Fogassi, L., Ferrari, P.F., Gesierich, B., Rozzi, S., Chersi, F., Rizzolatti, G., 2005. Parietal lobe: from action organization to intention understanding. Science (New York, NY) 308 (5722), 662–667, http://dx.doi.org/10.1126/science.1106138.

Gangitano, M., Mottaghy, F.M., Pascual-Leone, A., 2001. Phase-specific modulation of cortical motor output during movement observation. Neuroreport 12 (7), 1489–1492 ⟨http://www.ncbi.nlm.nih.gov/pubmed/11388435⟩.

Gastaut, H.J., Bert, J., 1954. EEG changes during cinematographic presentation; moving picture activation of the EEG. Electroencephalogr. Clin. Neurophysiol. 6 (3), 433–444 ⟨http://www.ncbi.nlm.nih.gov/pubmed/13200415⟩.

Grezes, J., 1998. Top down effect of strategy on the perception of human biological motion: a pet investigation. Cognit. Neuropsychol. 15 (6-8), 553–582, http://dx.doi.org/10.1080/026432998381023.

Hari, R., 2002. Brain rhythms and reactivity of the human motor cortex. International Congress Series 1226 (null), 87–95 (doi:10.1016/S0531-5131(01)00499-X).

Hari, R., 2006. Action-perception connection and the cortical mu rhythm. Prog. Brain Res. 159, 253–260, http://dx.doi.org/10.1016/S0079-6123(06)59017-X.

Herwig, U., Satrapi, P., Schönfeldt-Lecuona, C., 2003. Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. Brain Topogr. 16 (2), 95–99 ⟨http://www.ncbi.nlm.nih.gov/pubmed/14977202⟩.

Iacoboni, M., Dapretto, M., 2006. The mirror neuron system and the consequences of its dysfunction. Nat. Rev. Neurosci. 7 (12), 942–951, http://dx.doi.org/10.1038/nrn2024.

Keel, J.C., Smith, M.J., Wassermann, E.M., 2001. A safety screening questionnaire for transcranial magnetic stimulation. Clin. Neurophysiol. Off. J. Int. Federation of Clin. Neurophysiol. 112 (4), 720 ⟨http://www.ncbi.nlm.nih.gov/pubmed/11332408⟩.

Kim, 2007. Cortical localization of scalp electrodes on three-dimensional brain surface using frameless stereotactic image guidance system. J. Korean Neurol. Assoc. 25 (2), 155–160 ⟨http://www.koreamed.org/SearchBasic.php?RID=0031JKNA/2007.25.2.155&DT=1⟩.

Klimesch, W., 1999. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Research. Brain Res. Rev. 29 (2–3), 169–195 ⟨http://www.ncbi.nlm.nih.gov/pubmed/10209231⟩.

Klimesch, Wolfgang, Sauseng, P., Gerloff, C., 2003. Enhancing cognitive performance with repetitive transcranial magnetic stimulation at human individual alpha frequency. Eur. J. Neurosci. 17 (5), 1129–1133 ⟨http://www.ncbi.nlm.nih.gov/pubmed/12653991⟩.

Martineau, J., Andersson, F., Barthélémy, C., Cottier, J.-P., Destrieux, C., 2010. Atypical activation of the mirror neuron system during perception of hand motion in autism. Brain Res. 1320, 168–175, http://dx.doi.org/10.1016/j.brainres.2010.01.035.

Molenberghs, P., Cunnington, R., Mattingley, J.B., 2012. Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. Neurosci. Biobehav. Rev. 36 (1), 341–349, http://dx.doi.org/10.1016/j.neubiorev.2011.07.004.

Muthukumaraswamy, S.D., Johnson, B.W., 2004. Primary motor cortex activation during action observation revealed by wavelet analysis of the EEG. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 115 (8), 1760–1766, http://dx.doi.org/10.1016/j.clinph.2004.03.004.

Oberman, L.M., Hubbard, E.M., McCleery, J.P., Altschuler, E.L., Ramachandran, V.S., Pineda, J.A., 2005. EEG evidence for mirror neuron dysfunction in autism spectrum disorders. Brain Res. Cognit Brain Res. 24 (2), 190–198, http://dx.doi.org/10.1016/j.cogbrainres.2005.01.014.

Perry, A., Bentin, S., 2009. Mirror activity in the human brain while observing hand movements: a comparison between EEG desynchronization in the mu-range and previous fMRI results. Brain Res. 1282, 126–132, http://dx.doi.org/10.1016/j.brainres.2009.05.059.

Pfurtscheller, G., Aranibar, A., 1979. Evaluation of event-related desynchronization (ERD) preceding and following voluntary self-paced movement. Electroencephalogr. Clin. Neurophysiol. 46 (2), 138–146 ⟨http://www.ncbi.nlm.nih.gov/pubmed/86421⟩.

Pfurtscheller, G., Lopes da Silva, F.H., 1999. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 110 (11), 1842–1857 ⟨http://www.ncbi.nlm.nih.gov/pubmed/10576479⟩.

Pineda, J.A., 2005. The functional significance of mu rhythms: translating "seeing" and "hearing" into "doing". Brain Res. Brain Res. Rev. 50 (1), 57–68, http://dx.doi.org/10.1016/j.brainresrev.2005.04.005.

Puzzo, I., Cooper, N.R., Cantarella, S., Russo, R., 2011. Measuring the effects of manipulating stimulus presentation time on sensorimotor alpha and low beta reactivity during hand movement observation. NeuroImage 57 (4), 1358–1363, http://dx.doi.org/10.1016/j.neuroimage.2011.05.071.

Puzzo, I., Cooper, N.R., Vetter, P., Russo, R., 2010. EEG activation differences in the pre-motor cortex and supplementary motor area between normal individuals with high and low traits of autism. Brain Res. 1342, 104–110, http://dx.doi.org/10.1016/j.brainres.2010.04.060.

Puzzo, I., Cooper, N.R., Vetter, P., Russo, R., Fitzgerald, P.B., 2009. Reduced cortico-motor facilitation in a normal sample with high traits of autism. Neurosci. Lett. 467 (2), 173–177, http://dx.doi.org/10.1016/j.neulet.2009.10.033.

Raymaekers, R., Wiersema, J.R., Roeyers, H., 2009. EEG study of the mirror neuron system in children with high functioning autism. Brain Res. 1304, 113–121, http://dx.doi.org/10.1016/j.brainres.2009.09.068.

Rizzolatti, G, Fadiga, L., Gallese, V., Fogassi, L., 1996. Premotor cortex and the recognition of motor actions. Brain Res. Cognit. Brain Res. 3 (2), 131–141 ⟨http://www.ncbi.nlm.nih.gov/pubmed/8713554⟩.

Rizzolatti, G, Fogassi, L., Gallese, V., 2001. Neurophysiological mechanisms underlying the understanding and imitation of action. Nature Rev. Neurosci 2 (9), 661–670, http://dx.doi.org/10.1038/35090060.

Rizzolatti, Giacomo, Craighero, L., 2004. The mirror-neuron system. Annu. Rev. Neurosci. 27, 169–192, http://dx.doi.org/10.1146/annurev.neuro.27.070203.144230.

Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A., 2009. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 120 (12), 2008–2039, http://dx.doi.org/10.1016/j.clinph.2009.08.016.

Semlitsch, H.V, Anderer, P., Schuster, P., Presslich, O., 1986. A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP. Psychophysiology 23 (6), 695–703 ⟨http://www.ncbi.nlm.nih.gov/pubmed/3823345⟩.

Shah, D.B., Weaver, L., O'Reardon, J.P., 2008. Transcranial magnetic stimulation: a device intended for the psychiatrist's office, but what is its future clinical role?. Expert Rev. Med. Devices 5 (5), 559–566, http://dx.doi.org/10.1586/17434440.5.5.559.

Southgate, V., Hamilton, A.F., de, C., 2008. Unbroken mirrors: challenging a theory of Autism. Trends Cognit. Sci. 12 (6), 225–229, http://dx.doi.org/10.1016/j.tics.2008.03.005.

Please cite this article as: Puzzo, I., et al., The effect of rTMS over the inferior parietal lobule on EEG sensorimotor reactivity differs according to self-reported traits of autism in typically developing individuals. Brain Research (2013), http://dx.doi.org/10.1016/j.brainres.2013.10.016

Streltsova, A., Berchio, C., Gallese, V., Umilta, M.A., 2010. Time course and specificity of sensory-motor alpha modulation during the observation of hand motor acts and gestures: a high density EEG study. Exp. Brain Res. Exp. Hirnforsch. Exp. Cérébrale 205 (3), 363–373, http://dx.doi.org/10.1007/s00221-010-2371-7.

Szurhaj, W., Derambure, P., Labyt, E., Cassim, F., Bourriez, J.-L., Isnard, J., Guieu, J.-D., et al., 2003. Basic mechanisms of central rhythms reactivity to preparation and execution of a voluntary movement: a stereoelectroencephalographic study. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 114 (1), 107–119 ⟨http://www.ncbi.nlm.nih.gov/pubmed/12495771⟩.

Tiihonen, J., Kajola, M., Hari, R., 1989. Magnetic mu rhythm in man. Neuroscience 32 (3), 793–800 ⟨http://www.ncbi.nlm.nih.gov/pubmed/2601846⟩.

Wassermann, E.M., 1998. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation. Electroencephalography and clinical neurophysiology 108 (1), 1–16 ⟨http://www.ncbi.nlm.nih.gov/pubmed/9474057⟩.

Please cite this article as: Puzzo, I., et al., The effect of rTMS over the inferior parietal lobule on EEG sensorimotor reactivity differs according to self-reported traits of autism in typically developing individuals. Brain Research (2013), http://dx.doi.org/10.1016/j.brainres.2013.10.016