

Effects of prefrontal cortex damage on emotion understanding: EEG and behavioural evidence

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Humans are highly social beings that interact with each other on a daily basis. In these complex interactions, we get along by being able to identify others' actions and infer their intentions, thoughts and feelings. One of the major theories accounting for this critical ability assumes that the understanding of social signals is based on a primordial tendency to simulate observed actions by activating a mirror neuron system. If mirror neuron regions are important for action and emotion recognition, damage to regions in this network should lead to deficits in these domains. In the current behavioural and EEG study, we focused on the lateral prefrontal cortex including dorsal and ventral prefrontal cortex and utilized a series of task paradigms, each measuring a different aspect of recognizing others' actions or emotions from body cues. We examined 17 patients with lesions including ($n = 8$) or not including ($n = 9$) the inferior frontal gyrus, a core mirror neuron system region, and compared their performance to matched healthy control subjects ($n = 18$), in behavioural tasks and in an EEG observation—execution task measuring mu suppression. Our results provide support for the role of the lateral prefrontal cortex in understanding others' emotions, by showing that even unilateral lesions result in deficits in both accuracy and reaction time in tasks involving the recognition of others' emotions. In tasks involving the recognition of actions, patients showed a general increase in reaction time, but not a reduction in accuracy. Deficits in emotion recognition can be seen by either direct damage to the inferior frontal gyrus, or via damage to dorsal lateral prefrontal cortex regions, resulting in deteriorated performance and less EEG mu suppression over sensorimotor cortex.

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Abbreviations: IFG = inferior frontal gyrus; LPFC = lateral prefrontal cortex; MNS = mirror neuron system; RMET = Reading the Mind in the Eyes

Introduction

As social creatures, human beings interact with each other on a daily basis. These complex interactions are enabled by our ability to identify others' actions and infer their intentions, thoughts, and feelings. Failing to do so is extremely costly: individuals with autism spectrum disorder, for ex-

ample, have difficulties understanding the intentions, thoughts, and feelings of others, and consequently suffer severe problems with social interactions. One of the major theories accounting for this critical ability assumes that the understanding of social signals is based on a primordial tendency to simulate observed actions by activating a perceptual-motor system and using this information to

estimate the actor's intentions or emotions (Carruthers and Smith, 1996). This line of thought emerged from the Perception-Action model, according to which, perception of a behaviour in another automatically activates one's own representations for the behaviour, and output from this shared representation automatically proceeds to motor areas of the brain where responses are prepared and potentially executed (de Waal, 2008).

Tentative support to this theory has been provided by the discovery of mirror neurons in the macaque monkey. These neurons discharge when the monkey does a particular goal-directed action and when it observes another individual (monkey or human) doing a similar action (Rizzolatti *et al.*, 1996). Neurons with mirror-like properties were found primarily in the ventral premotor cortex (F5) and around the anterior intra-parietal sulcus (aIPS) of the macaque (Di Pellegrino *et al.*, 1992; Gallese *et al.*, 1996; Rizzolatti *et al.*, 1996; Rizzolatti and Sinigaglia, 2010). Neuroimaging studies in humans found additional brain regions that, similar to the mirror neuron system (MNS) in the monkey, are activated on the one hand by motor performance and, on the other hand, by observing similar movements made by others. Such activity was found primarily in the inferior parietal lobule (IPL), and the inferior frontal gyrus (IFG), which is the equivalent of the monkey area F5 (Rizzolatti and Craighero, 2004; Fabbri-Destro and Rizzolatti, 2008; Rizzolatti and Sinigaglia, 2010). More recent studies refer to an 'extended' MNS, which emphasizes the role of the sensorimotor cortex within this network (Pineda, 2008).

EEG and MEG research have focused on mu rhythms, as a signal of motor simulation. Mu rhythms are EEG/MEG rhythms with dominant frequencies in the alpha (7–14 Hz) and beta (15–25 Hz) bands measured over the sensorimotor cortex (for reviews see Pineda, 2005; Hari, 2006). The power of these frequencies is reduced during the execution of a motor action and also during the observation of a similar action performed by another person (Cochin *et al.*, 1999; Nishitani and Hari, 2000; Muthukumaraswamy *et al.*, 2004). This electrophysiological characteristic led researchers to propose that mu suppression represents the recruitment of the human MNS, as this dual activation mode reflects the basic property of the monkeys' MNS (Pineda, 2005). It is still under debate whether mu suppression over the sensorimotor cortex is a signature of information received from the IFG, from other human MNS regions (e.g. parietal cortex), or represents activation of mirror neurons in the sensorimotor cortex itself (Hari and Kujala, 2009).

In the past two decades, research on the putative human MNS has flourished, and has been linked to almost every aspect of human cognition, including action understanding (Rizzolatti and Craighero, 2004; Rizzolatti and Sinigaglia, 2010), imitation (Iacoboni *et al.*, 2005; Iacoboni, 2009), motor learning (Stefan *et al.*, 2008), speech perception (Rizzolatti and Arbib, 1998), and language development (Arbib, 2005; Gallese, 2008; Corballis, 2010). It has also

been linked to the formation of key social skills such as understanding the intentions (Iacoboni *et al.*, 2005) and emotions of others (Dapretto *et al.*, 2006; Gallese *et al.*, 2007; Schulte-Rüther *et al.*, 2007). This initial work was followed by criticism regarding the necessity of these neurons in action and emotion understanding (Hickok, 2009; Decety, 2010). One of the main criticisms stated that if a frontal-parietal network is important for action and emotion recognition, damage to regions in this network should lead to deficits in these domains. Note, however, that challenging this criticism is not trivial. While there are patients with lesions that include MNS regions, these lesions are almost always unilateral, while research on the human MNS consistently reports bilateral activation (Rizzolatti and Craighero, 2004; Pineda, 2005; Rizzolatti and Sinigaglia, 2010). In other words, a patient with lesions to parts of the human MNS has a working human MNS in the undamaged hemisphere that may be sufficient for normal task performance (Voytek *et al.*, 2010). Moreover, there is vast agreement today that simulation is not the only way in which we understand others (Singer and Lamm, 2009; Zaki and Ochsner, 2013), and so different brain regions which contribute to our ability to understand others [such as the temporal parietal junction (TPJ); Saxe and Kanwisher, 2003] or ventromedial prefrontal cortex (vmPFC; Shamay-Tsoory *et al.*, 2009; Lewis *et al.*, 2011] might be recruited when patients with lesions to the classic human MNS attempt to understand the other.

Nevertheless, some evidence for a correlation between lesions to MNS regions and deficits in understanding others exists. Buxbaum *et al.* (2005) tested left hemisphere stroke patients on pantomime imitation and recognition tasks, and found strong relationships between object-related pantomime imitation and object-related pantomime recognition. Pazzaglia *et al.* (2008) asked 28 left hemisphere-damaged patients with or without limb and/or buccofacial apraxia and seven right hemisphere-damaged patients with no apraxia, to match sounds evoking human-related actions or non-human action sounds with specific visual pictures. Hand and mouth action-related sound recognition were specifically impaired in limb and buccofacial apraxia patients, respectively. Lesion mapping revealed that the left frontoparietal cortex was crucial for recognizing the sound of limb movements. By contrast, the left IFG and adjacent insular cortex were associated with recognition of buccofacial-related action sounds. These behavioural and neural double dissociations indicate that a multimodal mirror network is actively involved in the body part-specific motor mapping of limb and mouth action-related sounds, as well as in the execution of the very same actions. Frenkel-Toledo and colleagues (2016) studied the relationship between imitation failure in ideomotor apraxia and MNS functioning. Results showed that failure to imitate observed manual movements correlated with diminished mu suppression in patients with damage to the right IPL, and in patients with damage to the right IFG pars opercularis—areas where major components of the human

MNS are assumed to reside (Frenkel-Toledo *et al.*, 2016). Kalénine and colleagues (2010) reported data from 43 left hemisphere stroke patients in two action recognition tasks in which they heard and saw an action word (e.g. ‘hammering’) and selected from two video clips the one corresponding to the word. In the spatial recognition task, foils contained errors of body posture or movement. In the semantic recognition task, foils were semantically related. A whole-brain voxel-based lesion–symptom mapping analysis suggested that the semantic and spatial gesture recognition tasks were associated with lesioned voxels in the posterior middle temporal gyrus and IPL, respectively. The IFG, on the other hand, was not predictive of performance in any task, suggesting that previous claims regarding its role in action recognition may require refinement (Kalénine *et al.*, 2010).

Lastly, in one of the seminal studies on the neuroscience of empathy, Shamay-Tsoory and colleagues (2009) showed a double dissociation between emotional empathic abilities, measured by the ability to recognize various categories of emotional expressions from photographs of eyes reflecting the emotions, and cognitive perspective-taking abilities (also referred to as ‘mentalizing’ or ‘Theory of Mind’), measured by a second-order false belief task (evaluating one’s ability to understand what someone else thinks about what someone else thinks) (Stone *et al.*, 1998). The authors revealed that while only emotional empathy was damaged following lesions to the IFG, only cognitive perspective taking was damaged following damage to the vmPFC (Shamay-Tsoory *et al.*, 2004, 2009).

In the current behavioural and EEG study, we focused specifically on the lateral prefrontal cortex (LPFC) and used a series of paradigms, each measuring a different aspect of recognizing others actions or emotions from body cues. We examined 17 LPFC lesioned patients, including or not including the IFG (eight and nine patients, respectively), and compared their performance to matched healthy control subjects, in various behavioural tasks and in an EEG task measuring mu suppression. Two behavioural tasks included inferring actions or emotions from biological motion point-light displays, a third task involved inferring gestures from hand actions, and a fourth task involved inferring emotions from the eyes. The EEG task used was a common observation-execution task that has been used extensively before, and has been known to elicit mu suppression.

As all patients had an intact hemisphere, and the MNS is considered a bilateral system encompassing frontal, parietal and sensorimotor regions, we predicted the patients would do relatively well on all tasks, but would show longer reaction times and reduced accuracy compared to age-matched controls, as well as less mu suppression in the EEG task. Considering previous findings, we further hypothesized that LPFC lesions may have more effect on emotion recognition than on action or gesture recognition. Lastly, we predicted that mu suppression in the observation-execution task would correlate with behaviour in the behavioural tasks performed outside of the EEG recording session. As eight of the

patients had lesions extending to parts of the IFG, a core MNS region, we further evaluated whether the behavioural deficits are specific to IFG lesioned patients, and whether IFG damage specifically affects mu suppression.

Materials and methods

Lesion patients

Patients were recruited from and examined in two different sites. Eleven patients with LPFC lesions following a resection of a primary intracranial tumour (six in the right hemisphere) (Supplementary Table 1) were examined at the Oslo University Hospital, all were fluent in Norwegian. At the time of surgery all tumours were low grade and had no extension beyond the primary lesion site (as reconstructed in Fig. 1). Tumour patients were rescanned at the time of our testing. Two patients showed increase of their tumour with infiltration of the corpus callosum and were excluded from testing. There was no change in lesion size in the remaining subjects in the study. Six patients following a stroke (one in the right hemisphere) were examined at the University of California Berkeley, all were fluent in English. Both Institutional Review Boards gave their approval for the study. Patient inclusion was based on LPFC brain lesions indicated on pre-existing CT and/or MRI scans. Participants with a history of serious psychiatric disease, drug, or alcohol abuse requiring treatment, pre-morbid head injury, pre-/comorbid neurological disease, IQ < 85, substantial aphasia, visual neglect, or marked sensory impairment were excluded from participation. All patients were recruited at least 6 months following damage (resection of tumour or stroke), once they were in a stable neurological condition, and leading a relatively independent life. For other demographic information see Supplementary Table 1. Patients gave written informed consent before participating in the studies. Patients at Berkeley received payment for participation and transportation, and patients in Oslo received payment for transportation only.

As the human MNS literature emphasizes the role of the IFG, subjects were further divided into two groups: the IFG group, if damage involved the pars opercularis and the pars triangularis [Brodmann areas (BAs) 44, 45], and a group of patients with LPFC damage involving damage outside the IFG. Illustrations of the traced lesions are presented in Fig. 1A and B, along with lesion superimposition for each group (for the latter, lesions were flipped to the left hemisphere to enhance anatomical overlap). In eight cases, patients assigned to the IFG group had damage that extended to include portions of areas 44 and/or 45; in seven of those cases lesions involved areas 44 and 45, and in one patient, the damage was restricted to only area 45. Among patients assigned to the non-IFG group, lesions were in BA 6, 8, 9, 10, 11, 43, 46, and 47. All patients had unilateral lesions. The patient groups were compared to 18 healthy age-matched controls. A one-way ANOVA ensured that there was no significant age difference between the three groups [IFG mean = 45.62 (standard deviation, SD = 13.5), non-IFG mean = 47.22 (SD = 6.96), and Controls mean = 47.06 (SD = 15.15); $F(2,32) < 1$, $P = 0.971$]. All participants had at least 12 years of formal education (Supplementary Table 1).

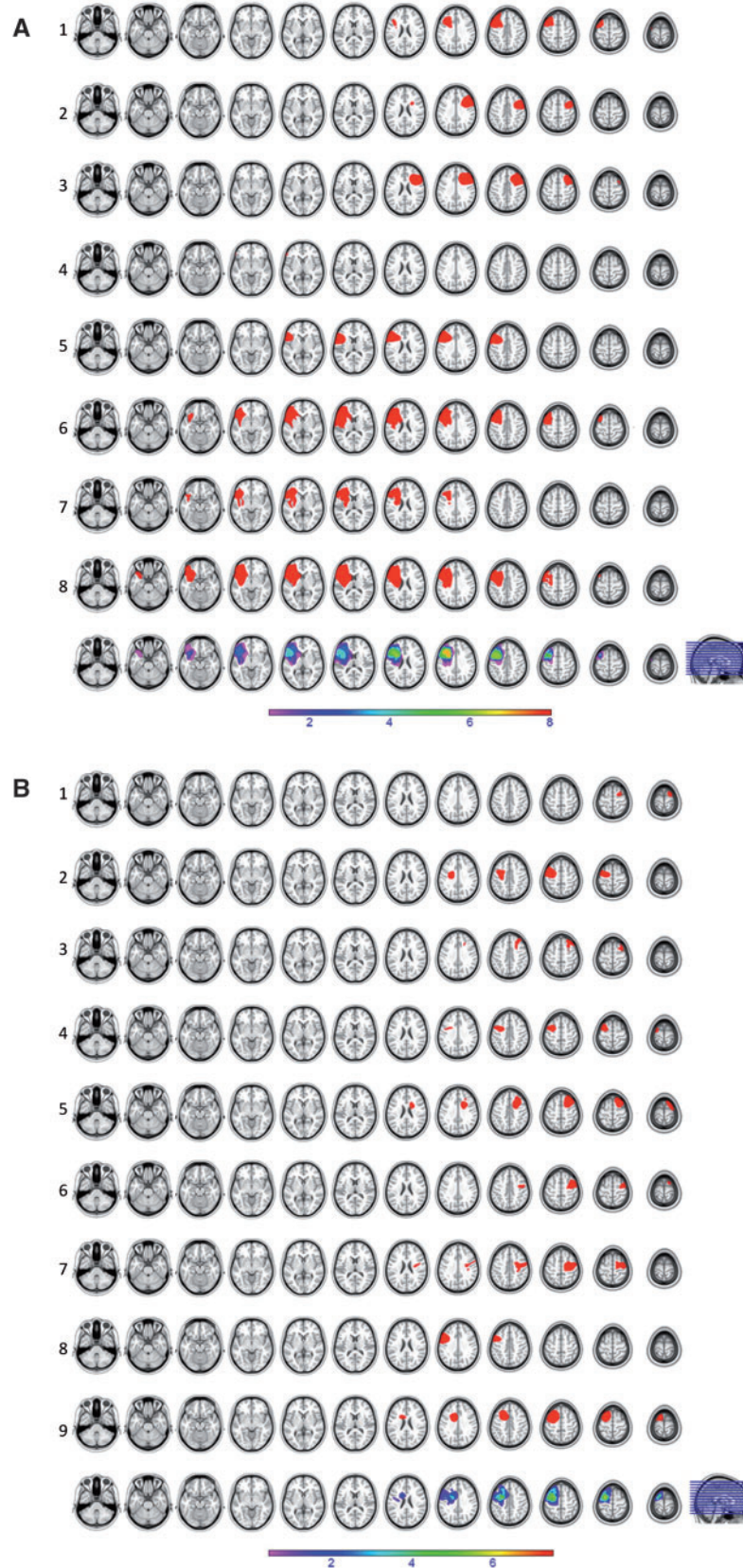


Figure 1 Reconstructions of lesions for both patient groups. (A) Individual IFG lesioned patients (Patients 1–8) and group overlay (bottom row). (B) Individual non-IFG lesioned patients (Patients 1–9) and group overlay (bottom row). The colour code for the group overlay indicates the number of patients with damaged tissue in that area.

Lesion reconstruction

Lesion reconstructions were based on structural MRIs obtained after study inclusion. Lesions were outlined by manually drawing on fluid attenuated inversion recovery (FLAIR), T₁- and T₂-weighted images of each participant's brain using MRICron (www.mccauslandcenter.sc.edu/mricro/mricron/) and Adobe Photoshop CC 2015 (<http://www.adobe.com/>). T₁, T₂ and FLAIR images were first co-registered to a T₁ MNI template (normalized from 152 T₁ scans), using Statistical Parametric Mapping software's (SPM8: www.fil.ion.ucl.ac.uk/spm/) New Unified Segmentation routine. The manual delineation of the lesions was performed on axial mosaics of the normalized T₁ scans. When available, high-resolution FLAIR and T₂-weighted images were used as aids to determine the borders of the lesions. The resulting lesion masks were converted to 3D MNI space using the Statistical Parametric Mapping software's (SPM8: www.fil.ion.ucl.ac.uk/spm/) Mosaic to Volume routine. Lesions were reconstructed under the supervision of a neurologist (R.T.K.). Illustrations of the traced lesions are presented in Fig. 1. We calculated lesion sizes using the MRICron descriptive statistics function after a lesion had been manually delineated.

Experimental design

Biological motion: actions

Participants were seated ~70 cm from a computer screen and instructed to name the action performed by figures in point-light display (PLD) video clips. Each movie depicted a human figure, represented by points of light at each joint, performing an action (painting, jumping, rowing, etc.). Ninety trials were presented in a sequential order. Each trial consisted of a 1000 ms fixation point, followed by a PLD video that repeated until the participant pressed the spacebar on a keyboard. Subjects were instructed to stop the video once they recognized the action, or decided they would be unable to identify the action. Response time was measured from the start of the video to the moment the participant stopped the video. After pressing the spacebar, the subject had unlimited time to verbally report the action they observed to an experimenter sitting in the room. Once ready, the subject pressed the spacebar again, starting the next trial.

Stimuli

The stimuli were taken from the database of Vanrie and Verfaillie (2004). Each PLD is composed of 13 dots placed at major joints of the human body, to create a figure that is visually impoverished but distinctly human and recognizable. By using these PLDs, cues from contour, texture, and facial expression are eliminated such that the subject can only focus on the biological motion of each action. The following 18 actions were selected from the database: crawl, cycle, drink, drive, jump, mow, paint, paddle, play pool, play tennis, row, salute, saw, spade, stir, sweep, walk, wave. Each of the 18 actions were shown at five distinct angles: 0° (head-on, as if facing the figure face-to-face), rotated 45° to the left and to the right, and 90° to the left and to the right. The duration of a single repetition of each video ranges from 666 ms to 4066 ms.

Measuring accuracy

When coding the responses, various similar definitions were acknowledged as the right answer to avoid influences of anomia, or other language difficulties. For example, for the action 'spade', the answers 'digging', 'shovelling', and 'making a hole' were also accepted. For the action 'mow', 'threshing weeds', 'cutting wheat', and 'scything wheat' were also accepted. For the action 'stir', 'scrubbing a pan' and 'wiping a counter' were also accepted.

Hand gestures

Participants were seated ~70 cm away from a computer screen and asked to correctly identify the meaning of various hand gestures. Participants were presented with a fixation point for 1000 ms followed by a 2000 ms video clip in which a hand gesture was performed. The following screen presented participants with a list of four numbered choices and asked what gesture was displayed. Reaction time was measured from the initial display of this screen and concluded when participants pressed the number corresponding with their answer on the keyboard. There were 88 trials presented in a random order.

Stimuli

The stimuli were created in Israel, but piloted in Berkeley and Oslo. Only gestures that had the same meaning and were well-known in both regions were used. The stimuli consisted of 2000 ms video clips that depicted a right or left hand of a male or female subject performing one of 11 hand gestures. Gestures included: there, bad, bye, come, go away, good, no, ok, sort of, stop and nothing (no meaning). Eight distinct videos were created for each gesture, varying the hand and sex of the actor. These original stimuli are available in the Supplementary material.

Biological motion: emotions

Subjects were seated ~70 cm from a computer screen with a keyboard in front of them. Emotion recognition was investigated using PLDs that depicted five different emotions. These impoverished stimuli allowed the investigation of the participants' ability to infer mental and emotional states from non-verbal behaviour. Participants were instructed to choose from a list of five options the emotion that best described each video they watched. Each trial consisted of a 1000 ms fixation point followed by a 3000 ms video clip. Next, a screen listing five numbered answer choices was displayed until the participant pressed the number key corresponding with their answer, prompting the start of the next trial. There were 35 trials presented in random order.

Stimuli

The emotions depicted in the videos include: anger, happiness, sadness, fear, and disgust. Each emotion was represented in seven different video clips, resulting in a total of 35 trials. Stimuli were created and previously described by Atkinson *et al.* (2004).

Reading the Mind in the Eyes Test

The Reading the Mind in the Eyes (RMET) is a validated test measuring the ability to correctly attribute mental state to facial expressions, when only the eyes are visible. It is thought

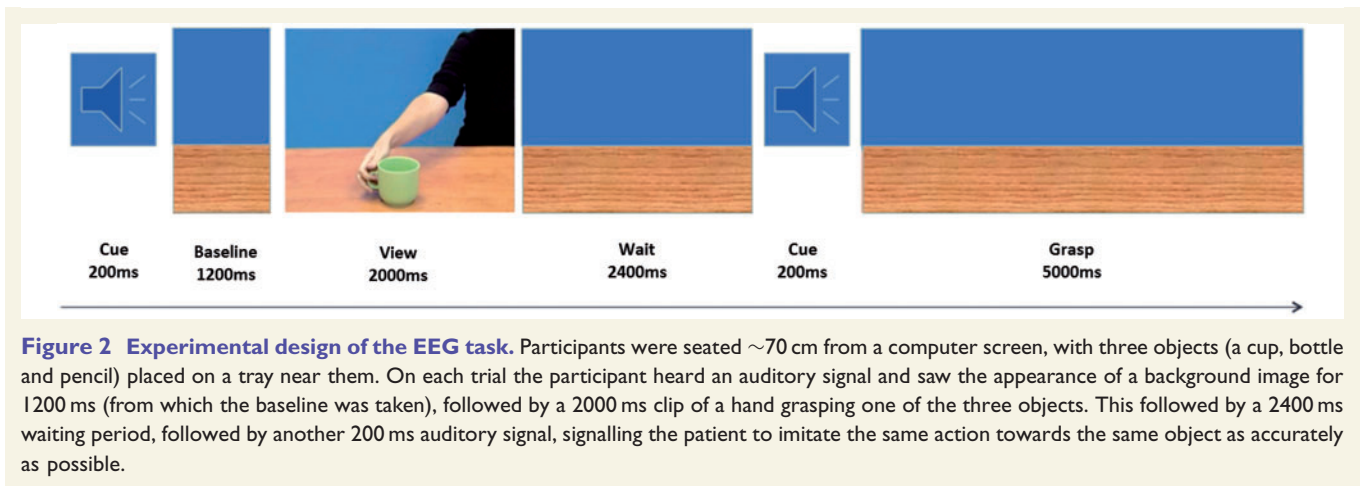


Figure 2 Experimental design of the EEG task. Participants were seated ~70 cm from a computer screen, with three objects (a cup, bottle and pencil) placed on a tray near them. On each trial the participant heard an auditory signal and saw the appearance of a background image for 1200 ms (from which the baseline was taken), followed by a 2000 ms clip of a hand grasping one of the three objects. This followed by a 2400 ms waiting period, followed by another 200 ms auditory signal, signalling the patient to imitate the same action towards the same object as accurately as possible.

to measure social sensitivity and has been shown to negatively correlate with autistic traits (Baron-Cohen *et al.*, 2001). In this test, participants are given a packet composed of 36 photographs of the eye area and one practice photo, each on a separate page. Four different emotions are written around each photo and participants are asked to choose the one that best describes what the person in the photo is feeling. Including the foils, 93 mental states are represented in the RMET, with 27 different target emotions (the correct response), of which 21 were presented only once. The photographs are balanced for sex. Participants were also supplied with a separate packet with the definitions of each emotion presented. The definitions were available for reference throughout the task to ensure the participants made informed selections. Participants verbally reported their answer selections to the experimenter sitting in the room. A validated Norwegian version of the RMET was used in Oslo (http://www.autismresearchcentre.com/arc_tests).

Observation and execution task with concurrent EEG

This is a classic task used in MNS studies, which has been shown to elicit mu suppression for both observation and execution in multiple studies (Perry and Bentin, 2009; Arnstein *et al.*, 2011; Frenkel-Toledo *et al.*, 2014, 2016). Participants were seated ~70 cm from a computer screen, with three objects (a cup, bottle and pencil) placed on a tray in front of them. In each trial, the participant heard an auditory signal (200ms), after which a background image appeared for 1200 ms from which the baseline was taken from, followed by a 2000 ms clip of a hand grasping one of the three objects. This was followed by a 2400 ms waiting period, followed by another 200 ms auditory signal, signalling the participants to imitate the same action towards the same object as accurately as possible (Fig. 2). The next trial began between 7000 to 7500 ms after the auditory signal, enabling enough time to perform the motor act and return to rest. There were 60 repetitions of View-Wait-Grasp trials in each session. The participants performed two sessions: one in which they saw a right hand and performed with their right hand, and one similarly with the left.

Stimuli

The experimental stimuli consisted of 2000 ms long video clips presenting a right or left hand of a male or a female reaching towards an object (a cup, bottle or pencil) and grasping it (adapted from Perry and Bentin, 2009). E-Prime2 was used for data presentation and response recording. These original stimuli are available in the Supplementary material.

Analysing motor execution

Videos were taken of the participants so that their arms and grasping actions were visible, but not their faces. Videos were later coded by a coder blind to the participant's group, on a point scale of 1 to 7, with 1 being no movement at all and 7 being a perfect imitation. Each trial began with a starting score of 7 and points were deducted at a set amount for various errors. One point was deducted for each of the following: hesitating or moving particularly slowly, bumping another object, repositioning the hand, not fully closing the hand around the object, or having an unsteady hand/arm. Two points were deducted for holding the hand in an unnatural position or for being overly stiff.

EEG acquisition and analysis

The EEG analogue signals were recorded continuously (from DC) by 64 Ag–AgCl pin-type active electrodes mounted on an elastic cap (BioSemi™) according to the extended 10–20 system, and from two additional electrodes placed at the right and left mastoids. All electrodes were referenced during recording to a common-mode signal (CMS) electrode between POz and PO3 and were subsequently re-referenced digitally (see below). Eye movements, as well as blinks, were monitored using bipolar horizontal and vertical electrooculography (EOG) derivations via two pairs of electrodes, one pair attached to the external canthi, and the other to the infraorbital and supraorbital regions of the right eye. Both EEG and EOG were digitally amplified and sampled at 512 Hz using a BioSemi Active II system (www.biosemi.com).

Data processing

Data were analysed using Brain Vision Analyzer software (Brain Products; www.brainproducts.com), and FieldTrip (Oostenveld *et al.*, 2011). Raw EEG data were initially high-pass filtered at

1 Hz and re-referenced offline to the digital average of the two mastoids. A notch filter was used at 60 Hz for data that were run in Berkeley and 50 Hz for the data run in Oslo. EEG deflections resulting from eye movements and blinks were corrected using an ICA procedure. Remaining artefacts exceeding $\pm 100 \mu\text{V}$ in amplitude were rejected. Following artefact rejection, data were low-pass filtered at 30 Hz.

We analysed the grasping movements as well as the video segments starting 0.5 s after the cue signalling the beginning of movement (and in the clip when actual motor movement begins) and up to 3 s for grasping / the end of the clips (2 s) for viewing. These were analysed in 0.5 s segments. Integrated power in the lower mu/alpha (7–14 Hz) and higher mu/beta (15–25 Hz) range was computed using a Fast Fourier Transform (FFT) performed at 0.5 Hz intervals (using a Hanning window). The segments were then averaged for each condition. A suppression index was calculated as the logarithm of the ratio of the power during each condition relative to the power during the baseline condition, and used as a dependent variable. The ratio (as opposed to a simple subtraction) was used to control for the variability in absolute EEG power as a result of individual differences such as scalp thickness and electrode impedance. The log transform was applied to the ratio before statistical analyses because ratio data are inherently not normally distributed as a result of lower bounding. A log ratio of <0 indicates suppression in the EEG amplitude, whereas a value of zero indicates no change and values >0 indicate enhancement. Suppression was computed around two central sites, C3 (including C3, C5, C1, FC3, CP3) and C4 (including C4, C2, C6, FC4, CP4), where mu suppression is measured. Since mu suppression is a bilateral phenomenon (Hari, 2006), we compared suppression in the lesioned versus non-lesioned hemisphere, for observation and execution conditions, which were either contralateral or ipsilateral to the lesion (i.e. ‘contra-lesional’, ‘ipsi-lesional’). These were compared to the average of left and right mu suppression in controls. To rule out a general attentional deficit, occipital alpha suppression (7–14 Hz, in electrodes O1 and O2) (Sauseng *et al.*, 2005) was calculated as well, in an identical manner to the above, and compared between the groups.

Results

Behavioural tasks

Lesion aetiology and task performance

In accordance with previous studies (Krämer *et al.*, 2013; Cipolotti *et al.*, 2015), lesion aetiology [stroke ($n = 6$); tumour ($n = 11$)] did not affect task performance on any of the tasks ($P = 0.057$ for Biological motion – Action accuracy, with tumour patients performing better than stroke patients; $P > 0.13$ for all other tasks).

Age and task performance

Although age was matched between groups (Table 1), we nonetheless examined whether it correlated with performance in the different tasks. Age negatively correlated with accuracy in both biological motion tasks (actions

$r = -0.370$, $P < 0.05$; emotions $r = -0.366$, $P < 0.05$), and a positive correlation was close to significant with gestures reaction time ($r = 0.297$, $P = 0.093$). The rest of the correlations were not significant ($P > 0.2$).

Biological motion: actions

A one-way ANOVA was conducted comparing the three groups, separately for accuracy (% correct) and for reaction time. While there were no significant effects for accuracy [$F(2,32) < 1$], there was a significant effect of group in reaction time [$F(2,32) = 5.240$, $P < 0.05$]. *Post hoc* Bonferroni corrected pairwise comparisons revealed that both patient groups were slower than controls, with no significant difference between them (IFG reaction time $>$ Controls, $P < 0.05$; non-IFG reaction time $>$ Controls, $P < 0.05$; Fig. 3). An additional analysis for accuracy, which included age as a covariate, yielded similar results [$F(3,29) = 2.00$, $P = 0.136$].

Hand gestures

As one IFG patient showed results that were -4.8 z-scores from the mean, this subject was removed from the analysis, resulting in seven IFG-lesioned patients, nine non-IFG lesioned patients and 18 control subjects who were tested on this task. A one-way ANOVA was conducted comparing the three groups, separately for accuracy (% correct) and for reaction time. While there was no significant group difference in accuracy [$F(2,31) = 1.337$, $P > 0.2$], there was a significant effect of group for reaction time [$F(2,31) = 6.648$, $P < 0.005$]. *Post hoc* Bonferroni corrected pairwise comparisons revealed that the IFG lesioned group was significantly slower than controls ($P < 0.05$) and the difference between non-IFG lesioned patients and control subjects did not reach significance ($P = 0.076$). An additional analysis for reaction time, which included age as a covariate, yielded similar results, however both groups now differed significantly from controls [$F(3,29) = 5.831$, $P < 0.005$ for group effect; IFG reaction time $>$ Controls, $P < 0.05$; non-IFG $>$ Controls, $P < 0.05$] (Fig. 3).

Biological motion: emotions

A one-way ANOVA was conducted comparing the three groups, separately for accuracy (% correct) and for reaction time. There was a significant effect for accuracy [$F(2,32) = 10.911$, $P < 0.001$]. *Post hoc* Bonferroni corrected pairwise comparisons revealed that both patient groups were worse than controls, with no significant difference between them (IFG $<$ Controls, $P < 0.05$; non-IFG $<$ Controls, $P < 0.001$). There was also a significant effect for reaction time [$F(2,32) = 4.266$, $P < 0.05$]. *Post hoc* Bonferroni corrected pairwise comparisons revealed that the IFG lesioned group was significantly slower than controls ($P < 0.05$), while the difference between non-IFG lesioned patients and control subjects was not significant ($P = 0.162$, Fig. 3). As sex differences are often seen in emotion recognition tasks, albeit the small

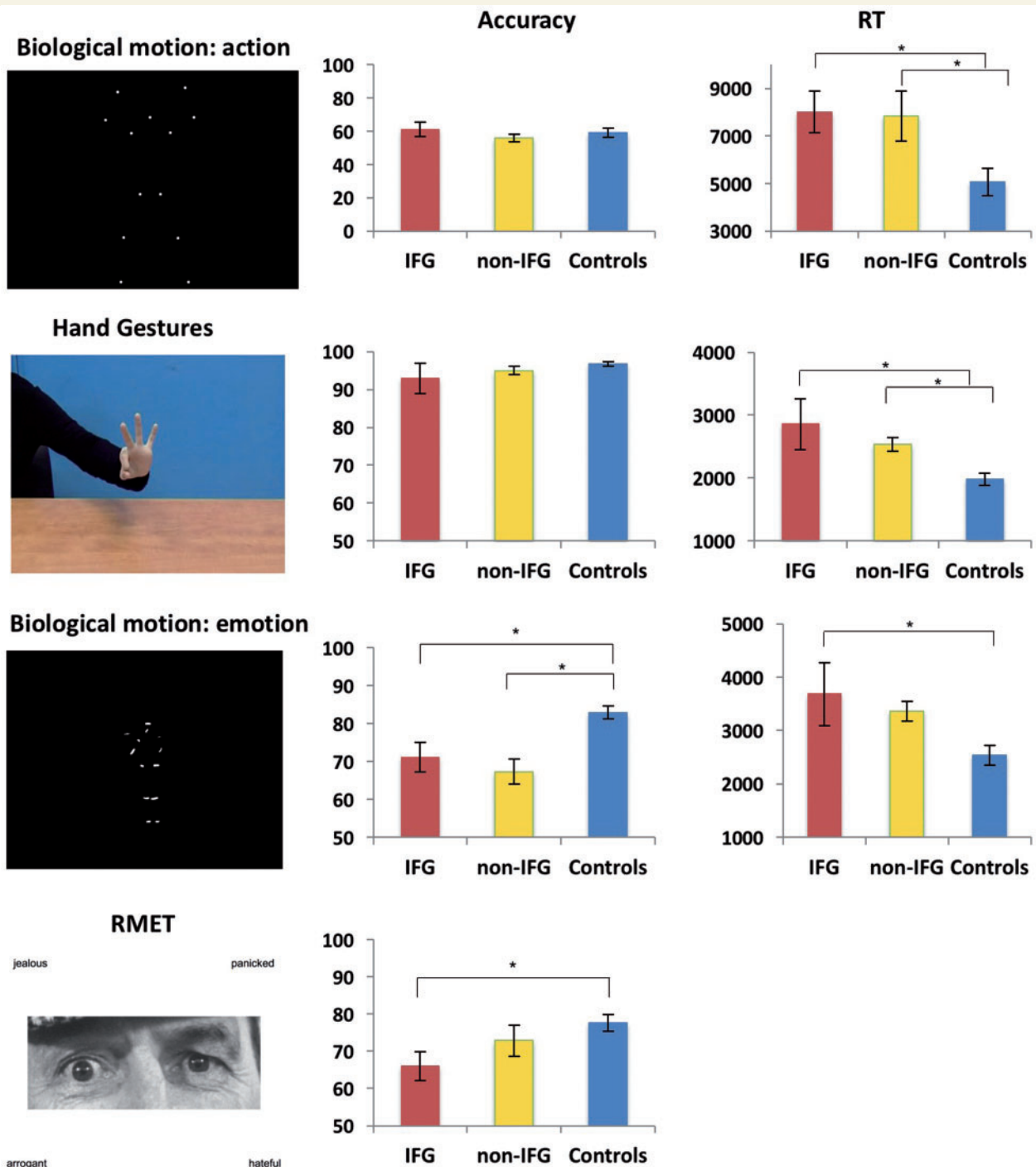


Figure 3 Accuracy (%) and response time (ms) for the three groups in all behavioural tasks. Error bars denote standard error of the mean (SEM). Note that for RMET, when taking sex into account in the model, there is still a significant effect of group; however, differences between controls and IFG patients are only close to significant ($P = 0.081$). RT = reaction time.

power of such a comparison considering the small number of participants, an additional analysis was run for accuracy, which included age as a covariate and sex as a fixed factor. This analysis revealed a significant effect for age [$F(1,28) = 11.664$, $P < 0.005$], and for sex [$F(1,28) = 4.488$, $P < 0.05$]; with female accuracy overall higher than males, but importantly yielded similar results

for group differences [$F(2,29) = 17.257$, $P < 0.0001$; *post hoc*: IFG < Controls, $P = 0.005$; non-IFG < Controls, $P < 0.0001$]. There was an additional interaction between group and sex, which we did not analyse further due to the small numbers in each group. Notably, the direction does not differ between lesion groups, but between lesions and controls, as controls show the opposite trend ($M > F$). For

results divided by males and females in each group, see Supplementary Table 2.

Reading the Mind in the Eyes test

A one-way ANOVA was conducted comparing the three groups for accuracy (% correct; reaction time is not measured in this test). There was a significant effect of Group [$F(2,28) = 17.257, P < 0.0001$]. *Post hoc* Bonferroni corrected pairwise comparisons revealed that the difference between the IFG lesioned group and controls was significant (IFG < Controls, $P < 0.05$), while there was no difference between the non-IFG lesioned patients and control subjects ($P = 0.822$) or between the patient groups ($P = 0.567$) (Fig. 3). Similar as above, as sex differences are often seen in emotion recognition tasks, albeit the small power of such a comparison considering the small number of participants, an additional analysis was run for accuracy, which included sex as a fixed factor. This analysis revealed a significant effect for sex [$F(1,29) = 9.558, P < 0.005$; with female accuracy overall higher than males], but importantly yielded similar results for group differences, with close to significant effects for the *post hoc* test comparing IFG to controls [$F(2,29) = 3.998, P < 0.05$; *post hoc*: IFG < Controls, $P = 0.081$; non-IFG < Controls, $P = 0.107$]. There was no interaction between group and sex. For results divided by males and females in each group, see Supplementary Table 3.

Observation and execution EEG task

Execution scores

Due to technical difficulties, we were unable to obtain video coverage of the hand actions of one IFG patient and one control subject. Performance was high in all groups with means as follows (scores are out of a maximum of 7): IFG group: right 6.47 (SD 0.99), left 6.88 (SD 0.04); non-IFG group: right 6.58 (SD 0.75), left 6.17 (SD 1.94); Controls: right: 6.82 (SD 0.13), left 6.79 (SD 0.22). A repeated measures ANOVA compared Execution with the left and right hands as within subject variables, and Group (IFG, non-IFG, Controls) as between-subject variable. There was no significant difference between hands [$F(1,30) < 1$], or between Groups [$F(2,30) < 1$], and no significant interaction [$F(2,30) = 0.126$]. There were two left-handed patients in the non-IFG group and one left-handed control subject. Controlling for handedness did not change these results. A similar analysis was run, looking for differences between the ipsi-lesional hand and the contra-lesional hand (with an average of right and left for control subjects). Means were: IFG group: Ipsi 6.83 (SD 0.11), Contra 6.53 (SD 1.00); non-IFG group: Ipsi 6.60 (SD 0.75), Contra 6.16 (SD 1.94); Controls: average of both hemispheres: 6.8 (SD 0.17). Again, no significant differences between groups were found, but there was a trend towards differences between ipsi-lesional and contra-lesional [$F(1,30) = 3.021, P = 0.092$], in the expected

direction, such that contra-lesional execution was less accurate than ipsi-lesional execution (mean 6.49 and 6.75, respectively).

EEG results

Lower mu/alpha band (7–14 Hz)

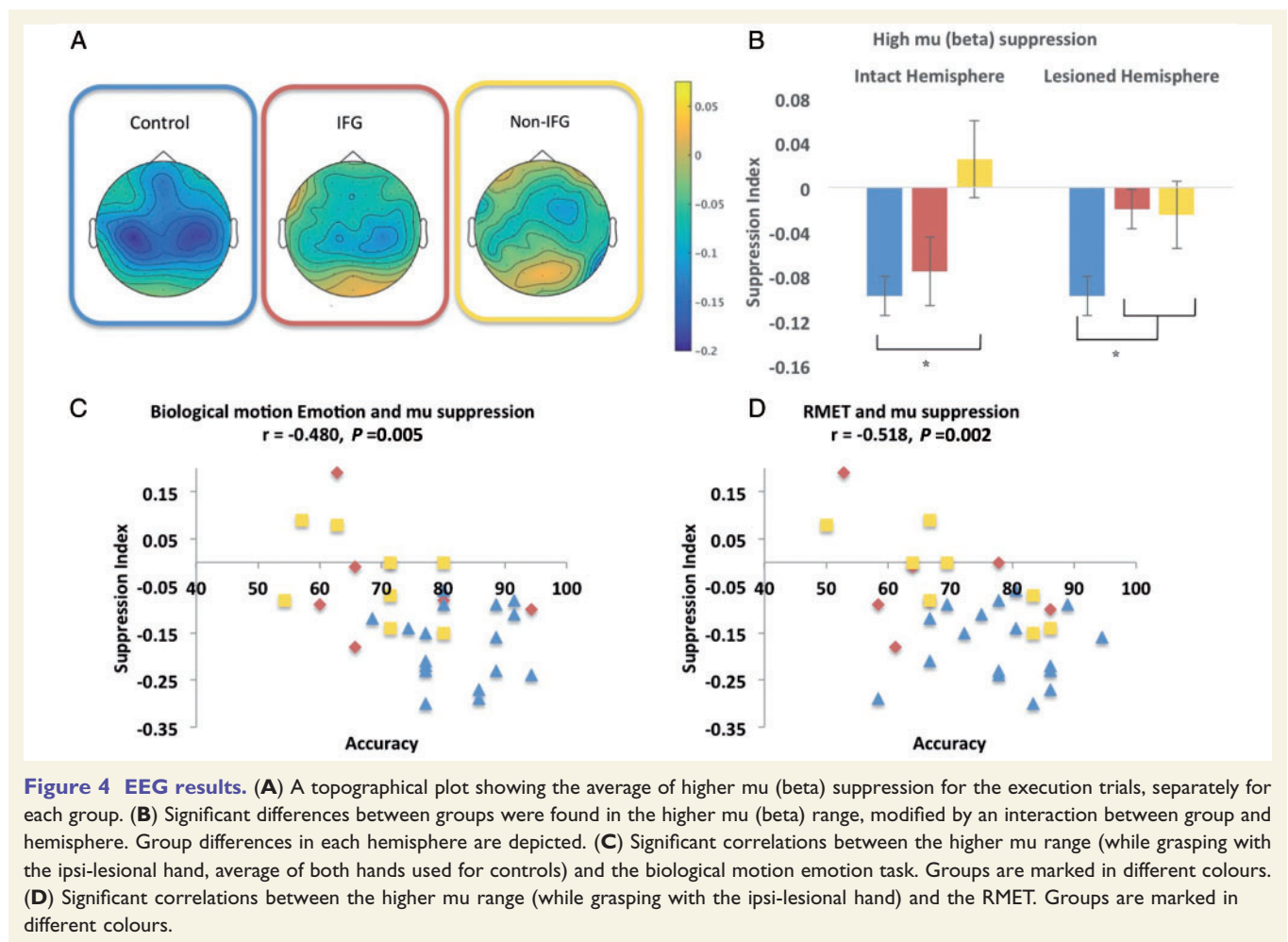
For technical reasons, there was one subject from each of the groups that did not complete the EEG task, resulting in seven IFG lesioned patients, eight non-IFG lesioned patients and 17 controls. ANOVA with Task (View, Grasp) × Hand (Ipsi-lesional, Contra-lesional) × Hemisphere (Lesioned, Intact) as within-subject variables, and Group (IFG, non-IFG and controls) as a between-subject variable, revealed a significant effect for Task [$F(1,29) = 6.036, P < 0.05$], and for Hand [$F(1,29) = 15.413, P < 0.001$], modified by a significant interaction between Task × Hand [$F(1,29) = 6.839, P < 0.05$], and a second-order interaction between Task × Hand × Hemisphere [$F(1,29) = 5.512, P < 0.05$]. There was no main effect for Group [$F(1,2,29) = 2.438, P = 0.105$] and no significant interaction with Group; however, the interaction Task × Hemisphere × Group approached significance [$F(2,29) = 3.109, P = 0.06$]. As group differences were our main interest in this study, we do not report further analyses of the interactions.

Higher mu/beta band (15–25 Hz)

ANOVA with Task (View, Grasp) × Hand (Ipsi-lesional, Contra-lesional) × Hemisphere [Lesioned, Intact] as within-subject variables, and Group (IFG, non-IFG and controls) as a between-subject variable revealed a significant effect of hand [$F(1,29) = 9.770, P < 0.005$], modified by an interaction between Hand × Hemisphere [$F(1,29) = 5.594, P < 0.05$]. Importantly, analysis of the higher band also revealed a significant effect for Group [$F(2,29) = 5.845, P < 0.01$], modified by an interaction between Group × Hemisphere [$F(2,29) = 4.154, P < 0.05$] (Fig. 4A and B). Comparing suppression between the three groups separately for each hemisphere revealed significant differences in both the intact and lesioned hemispheres [intact hemisphere: $F(2,29) = 6.319, P = 0.005$; lesioned hemisphere: $F(2,29) = 4.396, P < 0.05$]. *Post hoc* Bonferroni corrected comparisons revealed that in the intact hemisphere the non-IFG group had significantly less suppression than Controls ($P < 0.005$) with no difference between the IFG group and Controls or between the patient groups. In the lesioned hemisphere there were close to significant differences between the non-IFG group and Controls ($P = 0.076$) and between the IFG group and Controls ($P = 0.064$). Collapsing the two lesioned groups resulted in a significant effect for Group [$F(1,30) = 9.064, P = 0.005$] (Fig. 4B). An interaction between Group × Hand × Hemisphere was near significant ($P = 0.066$, not further analysed).

Occipital alpha (7–14 Hz, above occipital sites)

To rule out a general attentional deficit, occipital alpha suppression was calculated for electrodes O1 and O2,



and compared between the groups. There were no differences between groups in either of the sites, in none of the four task conditions (all P 's > 0.1).

Correlation between behavioural performance and beta/high mu suppression in the lesioned hemisphere

To examine if the results in the behavioural tasks (conducted separately from the EEG task) correlated with EEG mu suppression, we examined the correlation for all subjects (patients and controls collapsed) between the two tasks that showed a difference in accuracy (biological motion: emotion, and RMET) and the higher-mu suppression in the lesioned hemisphere in the four different conditions (for controls, left and right hemispheres were averaged). We decided to look at the four conditions separately, as there was a trend towards an interaction between them in the EEG analysis, and so we hypothesized that they may reveal different information. This resulted in eight comparisons, and after Bonferroni correction for multiple comparisons, only a correlation with a $P < 0.00625$ would be considered significant. There were significant

negative correlations between suppression in the lesioned hemisphere when executing with the ipsi-lesional hand, and performance in the emotional tasks (biological motion: emotion accuracy: $r = -0.480, P = 0.005$; RMET: $r = -0.518, P = 0.002$) (Supplementary Table 4 and Fig. 4C and D). Both correlations imply that the more suppression one had during execution in the EEG task, the better they were at inferring emotions of others in the behavioural tasks. Similar, although weaker, effects were found when correlating behaviour in these tasks with suppression in the other three conditions (Supplementary Table 4). As the non-IFG lesioned group showed less mu suppression in the intact hemisphere as well, we ran a similar analysis with mu suppression in the intact hemisphere and found no significant correlations with behaviour in the emotion tasks (all $P > 0.05$, uncorrected).

Extent of brain damage

IFG group mean lesion volume was 71.98 mm^3 (SD 60.26) while the non-IFG group mean was 22.77 mm^3 (SD 14.17). The difference between them was close to significant ($P = 0.055$, equal variance not assumed). To examine whether the behavioural results were affected by the extent of damage

to the frontal cortex, we ran a correlation between extent of damage (lesion volume) and behaviour in all tasks. Lesion volume did not correlate significantly with performance in any of the tasks (all $P > 0.13$, except a trend-level association for biological motion: action, accuracy $P = 0.062$, uncorrected). As mu suppression may be affected by damage to BA6/BA8, and all lesion patients but one had some extent of damage to these regions, we also tested for a correlation between lesion volume in these regions and mu suppression in the lesioned hemisphere. There was no correlation between lesions to these regions and mu suppression in any of the conditions ($P > 0.084$ in all comparisons, uncorrected). There was also no difference between the two lesioned groups in the extent of damage to these regions ($P > 0.2$ for both).

Discussion

In the current behavioural and EEG study, we examined the effects of lesions to the LPFC, with or without IFG damage, on performance in a series of tasks measuring one's ability to recognize others' actions and emotions. Two of the tasks involved inference from point-light biological motion displays, one involved inferring actions, and one emotions. While neither lesion group showed deficits in inferring actions from these point-light displays (although both showed longer reaction times), both lesion groups showed a reduction in inferring emotions, with the IFG group showing an additional increase in reaction time. A third task showed whole hand movements from which human gestures had to be inferred. There were no group differences in accuracy in this task, but the IFG group had significantly longer reaction time relative to controls. A fourth, non-timed, task involved inferring emotions from images of the eyes (RMET), in which only the IFG group showed reduced accuracy.

It should be noted that the differences in performance between the tasks cannot be attributed to task difficulty. While there may have been a ceiling affect for performance in the gestures task, the Biological motion: actions task, in which there were no differences in accuracy, was reported by control subjects to be the most difficult. This can also be seen by the accuracy scores and reaction times of the control subjects, which were worse than in any other task. Similarly, the differences between groups cannot be explained by lesion volume, as lesion volume did not correlate with performance in any of the tasks.

One way to categorize these tasks is by the involvement of an emotional component in the task, i.e. whether it required understanding others emotions. The biological motion action task and the hand gestures task have no emotional component involved, while the biological motion emotion task and RMET clearly measure the ability to infer the emotions of others. Our results follow this categorization. While the non-emotional tasks resulted only in differences in reaction time, tasks with an emotional component resulted in reduced accuracy and, for the IFG

group, also prolonged reaction time. This result is in line with previous findings that highlighted the role of the IFG in emotional empathy (Kaplan and Iacoboni, 2006; Shamay-Tsoory, 2009). The fact that LPFC lesions resulted in clear deficits in tasks requiring recognition of others' emotions, without similar deficits for inferring actions, implies that inferring actions may rely on other regions, such as parietal regions and less on LPFC. It should be noted that neuroimaging studies do show activation in IFG and premotor regions in action recognition as well as in more cognitive perspective taking tasks (Iacoboni *et al.*, 2005; Gazzola *et al.*, 2006). However, activation in these regions does not mean that they are necessary for action recognition. This is in line with previous lesion studies showing effects of parietal, but not frontal, damage on action and gesture recognition (Kalénine *et al.*, 2010), as well as specific effects of IFG damage on emotional empathy (Shamay-Tsoory, *et al.*, 2009). Future studies could benefit from testing recognition of actions and emotions within the same task, thus enabling a direct comparison between them. In addition, testing patients with lesions to different subregions of the MNS (e.g. the inferior parietal lobe, or superior temporal sulcus), may enable further differentiation between the roles of subregions of this network in social cognition.

Notably, patients from both groups were still able to perform all tasks, albeit with declined performance. These results strengthen the notion that understanding emotions is not mediated by one brain region or network, but is more likely a product of activations in different regions, including the 'mentalizing network' [comprising vmPFC (Shamay-Tsoory *et al.*, 2009), the temporal parietal junction (Saxe and Kanwisher, 2003) and the superior temporal sulcus (STS; Gallagher and Frith, 2003)], the amygdala and insula, which have long been implicated in inferring emotional experiences (Carr *et al.*, 2003; Wicker *et al.*, 2003; Singer *et al.*, 2004; Leigh *et al.*, 2013), as well as regions of the human MNS in the intact hemisphere.

Although IFG lesioned patients showed differences from control subjects that were not seen in the non-IFG group (e.g. in the RMET), there was no significant difference between the lesioned groups. Moreover, deficits in understanding others emotional states were also seen in the LPFC lesioned group that did not include the IFG. This suggests that LPFC as a whole plays a crucial role in understanding emotions, or that these frontal lesions affect pathways to the other relevant regions, such as the sensorimotor and parietal regions (Pineda, 2008). Indeed, differences between controls and both lesion groups were evident in the EEG analysis. Analysis of mu suppression, an EEG signature for motor simulation measured over sensorimotor cortex, revealed differences between both lesioned groups and controls in the higher mu range, and the amount of suppression in the lesioned hemisphere negatively correlated with performance in the emotional behavioural tasks. While reduction in mu suppression could partially be a result of damage to motor regions or connections to these regions, it should be noted that damage to BA6 and BA8 did not correlate with mu suppression.

One caveat of this study is the uneven number of female and male patients in each patient group as there are known sex differences in emotion recognition tests in general, and specifically in the RMET (Baron-Cohen *et al.*, 2001, 2015). Importantly, while the female advantage replicated in our sample, it did not compromise the overall conclusion that LPFC lesions affect emotion recognition. However, the specific differences between the two lesion groups are less clear, as the IFG patient group had more male patients, and indeed the difference between the IFG group and controls only approached significance when taking sex into account. As male and female subjects were not equated in our sample for age, education or hemisphere damaged, we leave sex differences in lesion patients for future investigations.

An additional caveat is the uneven number of left and right lesioned patients. While human MNS activation is considered bilateral, previous work highlighted the role of the right hemisphere in processing emotion (Schwartz *et al.*, 1975; Ley and Bryden, 1979; Blonder *et al.*, 1991; Adolphs, 2002). The relatively small and unequal number of left and right lesioned patients does not allow us to differentiate between the two groups, leaving this for future investigation. This caveat also limits our interpretation of some of the EEG results. Specifically, note that the correlations between performance in the behavioural task and mu suppression over sensorimotor cortex were strongest when correlating with suppression for execution with one's ipsi-lesional hand. This is a puzzling result, since the lesioned hemisphere controls the contralateral hand. However, for the majority of patients (10/15), executing with the ipsi-lesional hand meant using their left, non-dominant hand, which for most people is more difficult to do. It may be the case that this more difficult task portrayed best the differences in mu suppression following LPFC lesions.

As noted in the 'Introduction' section, it is still under debate whether mu suppression over the sensorimotor cortex is a signature of information received from the IFG, from other human MNS regions, or represents activation of mirror neurons in the sensorimotor cortex itself (Hari and Kujala, 2009). Arnstein *et al.* (2011) measured EEG mu suppression simultaneously with functional MRI blood oxygen level-dependent signal in an observation-execution task, and showed a correlation between mu suppression and different regions of the human MNS, such as the inferior parietal lobe (IPL), dorsal premotor (dPM) and primary somatosensory cortex (BA2), but not with IFG. Similarly, in the current study, the correlation between mu suppression and performance in the emotional tasks was not specific to the IFG lesioned group, but existed across groups. As can be seen in Fig. 3C and D, patients from both lesion groups tended to have less suppression than control subjects, which then correlated with their behaviour in the emotional recognition tasks. The non-IFG group showed a significant reduction in mu suppression in the intact hemisphere as well. This may be a result of disturbed interhemispheric connections between the lesioned areas and the contralateral non-lesioned sensorimotor regions (Carter *et al.*, 2010; Gratton *et al.*, 2012;

Siegel *et al.*, 2016). Therefore, it seems that the reduction in mu suppression is not specific to IFG damage, and could have been caused by dysfunction in the sensorimotor cortex, e.g. via damage to other frontal regions with inputs to sensorimotor cortex. In line with this interpretation, previous research has linked the sensorimotor cortex to recognition of emotional stimuli, and lesions to this region to deficits in emotion recognition (Adolphs *et al.*, 2000; Heberlein *et al.*, 2004; Pourtois *et al.*, 2004; Pitcher *et al.*, 2008). Note that there was no lesion effect on occipital alpha suppression, which is considered a general signature of visual attention. Together with the high imitation scores, this strengthens the notion that deficits are not caused by a general attentional effect. That said, we cannot rule out that other cognitive processes may be affected by LPFC damage, that were not tested in this line of experiments.

Lastly, it should be noted that differences between groups were found only in the higher and not the lower mu range. While both rhythms have been shown to be affected by observing and executing goal-directed actions, several lines of evidence suggest that they have different sources. Both MEG and intracranial EEG recordings suggest that higher mu rhythms (~20 Hz) originate predominantly in the precentral primary motor cortex, while the lower rhythms (~10 Hz) originate in the postcentral primary somatosensory cortex (Hari, 2006). Hence, the proximity of structures generating higher mu rhythms to the LPFC may be the reason they are affected by lesions to frontal regions, while the lower mu rhythms were not. Proximity of the LPFC to the sensorimotor cortex may also explain why mu suppression is affected bilaterally in the non-IFG lesioned patients, and only in the lesioned hemisphere in the IFG-lesioned patients.

To conclude, these results provide strong support for the role of the human MNS in understanding others' emotions, by showing that even unilateral frontal lesions to this bilateral system result in deficits in both accuracy and reaction time in tasks involving the recognition of others' emotions. In tasks involving the recognition of actions, patients showed a general increase in reaction time, which may not be related specifically to LPFC. The emotion recognition deficits can be acquired by either direct damage to the IFG, or via damage to other LPFC regions, resulting in less activation in the sensorimotor cortex, measured by EEG mu suppression.

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Supplementary material

Supplementary material is available at *Brain* online.

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