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Research report

# Lesion evidence for a human mirror neuron system

Ellen Binder [a,b,*], Anna Dovern [a,b], Maike D. Hesse [a,b], Markus Ebke [c], Hans Karbe [d], Jochen Saliger [d], Gereon R. Fink [a,b] and Peter H. Weiss [a,b]

[a] Department of Neurology, University Hospital Cologne, Cologne, Germany
[b] Institute of Neuroscience and Medicine (INM-3), Research Centre Juelich, Juelich, Germany
[c] Department of Neurology, Dr. Becker Rhein-Sieg-Klinik, Nümbrecht, Germany
[d] Neurological Rehabilitation Centre Godeshöhe, Bonn, Germany

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ABSTRACT

More than two decades ago, the mirror neuron system (MNS) was discovered in non-human primates: Single-cell recordings detected visuo-motor neurons that discharged not only when the monkey performed an action, but also when it observed conspecifics performing the same action. It has been proposed that a fronto-parietal circuitry constitutes the human homolog of the MNS. However, the functional role of a human MNS (i.e., whether it is functionally necessary for imitation or action understanding) to date remains controversial. We here examined how patients with left hemisphere (LH) stroke imitate, recognize, and comprehend intransitive meaningful limb actions. In particular, we investigated whether apraxic patients with lesions affecting key nodes of the putative human MNS show deficits in action imitation, action recognition, and action comprehension to a similar degree – as predicted by the MNS hypothesis. Behavioral results showed that patients with apraxia ($n = 18$) indeed performed significantly worse in all three motor cognitive tasks compared to non-apraxic patients ($n = 26$) and healthy controls ($n = 19$), whose performance did not differ significantly. Lesions of the apraxic (compared to non-apraxic) patients with LH stroke affected more frequently key regions of the putative human MNS, i.e., the left inferior frontal, superior temporal, and supramarginal gyri as well as the inferior parietal lobe ($p < .01$, false discovery rate – FDR-corrected). Albeit largely overlapping, voxel-based lesion-symptom mapping (VLSM) revealed that deficits in gesture comprehension were mainly associated with lesions of more anterior parts of the MNS, whereas lesions located more posteriorly mainly resulted in gesture imitation deficits ($p < .05$, FDR-corrected). Our clinical data support key hypotheses derived from the notion of a human MNS: LH lesions to the MNS core regions affected – critically and to a similar extent – the imitation, recognition, and comprehension of meaningful actions.



* *Corresponding author*. Department of Neurology, University Hospital Cologne, Kerpener Straße 62, 50937 Cologne, Germany.
E-mail address: ellen.binder@uk-koeln.de (E. Binder).

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## 1. Introduction

In 1992, di Pellegrino, Fadiga, Fogassi, Gallese, and Rizzolatti were the first to describe in the macaque a special class of visuo-motor neurons that were activated both during the execution of an action as well as during the observation of the same motor act performed by another individual. Cells with this so called "mirror neuron property" where first found in the ventral premotor cortex (area F5) and subsequently also within area PF/PFG of the inferior parietal lobule [see for example Casile (2013), Cattaneo and Rizzolatti (2009), Kilner and Lemon (2013)]. In humans, numerous neuroimaging studies reported blood oxygenation level dependent (BOLD) signal changes during action observation and action execution in brain regions broadly consistent with the idea of the existence of a human mirror neuron system (hMNS), as demonstrated in recent meta-analyses (Caspers, Zilles, Laird, & Eickhoff, 2010; Molenberghs, Cunnington, & Mattingley, 2009, 2012). Core regions of this putative hMNS are believed to constitute a fronto-parietal circuitry, which comprises the posterior inferior frontal gyrus [IFG, with the pars opercularis (Brodmann area – BA 44) as a homolog of monkey area F5], and the rostral inferior parietal lobule (IPL, as a homolog of monkey area PF/PFG), supplemented by higher-order visual processing of observed actions in the superior temporal sulcus (STS) (Cattaneo & Rizzolatti, 2009; Glenberg, 2011; Iacoboni, 2005; Molenberghs et al., 2009). However, direct evidence for the existence of a hMNS to date remains scarce as neuronal recordings in humans were limited to medial frontal and temporal cortices due to clinical restrictions (Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010). Other methodological approaches, e.g., multi-voxel pattern analysis of functional magnetic resonance imaging (fMRI) data (Oosterhof, Wiggett, Diedrichsen, Tipper, & Downing, 2010) and repetition suppression (Kilner, Neal, Weiskopf, Friston, & Frith, 2009) provided evidence for brain areas with responses compatible with the idea of mirror neurons in the human parietal, occipito-temporal and IFG. Apart from neuro-anatomical aspects, there is an ongoing debate about the functional relevance of a hMNS (Hickok, 2009) ranging from motor learning (Cattaneo & Rizzolatti, 2009) over language acquisition (Arbib, 2005) to social cognition (Rizzolatti & Fabbri-Destro, 2008; Rizzolatti, Fabbri-Destro, & Cattaneo, 2009). Nevertheless, the basic "mirror mechanism" is supposed to map the perceived actions directly onto the observer's own motor system. It is assumed that this mapping does not only refer to low-level features of the action (e.g., kinematics), but also the action's goal (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996). While the mapping of low-level features supports action imitation processes, the mapping of action goals additionally enables the understanding of an observed motor act (Hesse, Sparing, & Fink, 2009; Iacoboni, 2005; Rizzolatti & Fabbri-Destro, 2008).

Apraxia, a disorder of motor cognition, presents with deficits in the performance of purposeful skilled movements – including imitation – that cannot simply be accounted for by primary motor, sensory, or aphasic deficits (Dovern, Fink, & Weiss, 2012; Foundas, 2013). Apraxia is frequently observed after left hemisphere (LH) stroke involving frontal and parietal areas and affects both the ipsi- and contralesional limbs (Goldenberg, 2009). In addition to deficits in performing complex actions, action observation deficits, i.e., disturbed recognition and understanding of purposeful limb movements, e.g., a gesture, have also been described (Buxbaum, Kyle, & Menon, 2005; Heilman, Rothi, & Valenstein, 1982; Pazzaglia, Pizzamiglio, Pes, & Aglioti, 2008; Pazzaglia, Smania, Corato, & Aglioti, 2008; Rothi, Heilman, & Watson, 1985). Therefore, LH stroke patients with apraxia offer a unique framework for investigating core functions of a putative hMNS. Furthermore, in contrast to correlative neuroimaging studies, investigating the effect of brain lesions offers insights into causality relating brain structures to specific cognitive function (Avenanti, Candidi, & Urgesi, 2013; Urgesi, Candidi, & Avenanti, 2014).

Accordingly, we investigated with the help of LH stroke patients (with and without apraxia), whether structures assumed to be core parts of the hMNS are critically involved in imitating, recognizing, and understanding actions. Unlike previous studies, we are the first to use the identical set of 40 meaningful intransitive limb gestures for three different motor cognitive tasks: (i) the *recognition* of a correctly performed gesture, (ii) the *comprehension* of the gesture's meaning, and (iii) the *imitation* of the given gesture. One of the key predictions resulting from the putative existence of a hMNS is that damage to its core regions should affect the recognition, understanding and imitation of actions to similar degrees. Thus, if the prediction holds true, then apraxic stroke patients with lesions affecting the key nodes of the putative hMNS (i.e., IFG, IPL and possibly STS) should exhibit similar deficits in these different motor cognitive domains.

## 2. Material and methods

### 2.1. Participants

A total of 53 patients suffering from a single (first ever) unilateral ischemic stroke affecting the LH participated after giving written informed consent. Patients were consecutively recruited during the subacute or chronic stage from the Department of Neurology, University Hospital Cologne ($n = 25$), the Rehabilitation Centre (Dr. Becker Rhein-Sieg-Klinik) in Nümbrecht ($n = 15$), or the Neurological Rehabilitation Centre Godeshöhe, Bonn ($n = 13$). Nine patients had to be excluded from further analysis due to additional right hemispheric lesions ($n = 5$), left-handedness ($n = 1$), refusal of neuropsychological assessment ($n = 1$), or lack of lesion demarcation in clinical imaging despite persisting neurological and neuropsychological deficits ($n = 2$). The remaining 44 LH stroke patients (29 male, mean age 60.8 years, range 30–80 years) fulfilled the inclusion criteria, i.e., right-handedness according to the Edinburgh Inventory of Manual Preference (Oldfield, 1971), age 18–80 years, sufficient knowledge of German, absence of severe language comprehension deficits (i.e., preventing subjects from understanding the study procedure and tasks), and no history of any other neurological or psychiatric disorder. Nineteen right-handed volunteers (11 male, mean age 57.8 years, range 34–72 years) with no history of neurological, psychiatric or relevant orthopedic disease served as healthy controls. Patients and control subjects did not differ with respect to age [$t(61) = .91$, $p = .365$]. The study