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Review

Does dysfunction of the mirror neuron system contribute to symptoms in amyotrophic lateral sclerosis?

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HIGHLIGHTS

- Mirror neurons are a fascinating class of neurons that are active during action and observation of the same action.
- Mirror neurons and the mirror neuron system could be of fundamental importance in social cognition, as well as functioning in the processes of motor control and motor learning.
- In ALS, the mirror neuron system might be implicated in, the split-hand syndrome, gait, empathy, speech, and related language–gesture impairments.

ABSTRACT

There is growing evidence that mirror neurons, initially discovered over two decades ago in the monkey, are present in the human brain. In the monkey, mirror neurons characteristically fire not only when it is performing an action, such as grasping an object, but also when observing a similar action performed by another agent (human or monkey). In this review we discuss the origin, cortical distribution and possible functions of mirror neurons as a background to exploring their potential relevance in amyotrophic lateral sclerosis (ALS). We have recently proposed that ALS (and the related condition of frontotemporal dementia) may be viewed as a failure of interlinked functional complexes having their origins in key evolutionary adaptations. This can include loss of the direct projections from the corticospinal tract, and this is at least part of the explanation for impaired motor control in ALS. Since, in the monkey, corticospinal neurons also show mirror properties, ALS in humans might also affect the mirror neuron system. We speculate that a defective mirror neuron system might contribute to other ALS deficits affecting motor imagery, gesture, language and empathy.

Contents

Abbreviations: ALS, amyotrophic lateral sclerosis; ADM, abductor digiti minimi; APB, abductor pollicis brevis; bvFTD, behavioral variant of frontotemporal dementia; FTD, frontotemporal dementia; fMRI, functional MRI; MNS, mirror neuron system; M1, primary motor cortex; PTNs, pyramidal tract neurons; vMPFC, ventral medial prefrontal cortex.

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1. Introduction

The human motor system has been critically refined through evolution and is profoundly interconnected to the many other brain networks. Motor system degeneration, involving loss of limb function, gait, speech and vocalization are the clinical hallmarks of the adult neurodegenerative disorder amyotrophic lateral sclerosis (ALS), and can be understood, to an extent, by this evolutionary development (Eisen et al., 2014b). Although, typically confined to a body region at disease onset, there may be a rapid coalescence of regional involvement involving upper and lower motor neuron loss, resulting in a characteristic clinical syndrome, termed ALS (Hardiman et al., 2011; Kiernan et al., 2011). Respiratory failure is the terminal event in the majority of patients, a characteristic feature of ALS that is absent in most other neurodegenerations. ALS also affects extramotor systems, involving clinical, pathological and genetic overlap with frontotemporal dementia (FTD), most commonly through expansions of the hexanucleotide repeat in *C9orf72* (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Members of the same family may develop relatively 'pure' FTD, ALS or both, thus broadening the clinical syndrome of ALS (Snowden et al., 2013).

The incidence of frank dementia in sporadic ALS is approximately 15%, but a much higher proportion of patients show sub-clinical evidence of executive dysfunction (Lillo et al., 2011). Executive functions, free verbal recall and naming are the most affected cognitive deficits in ALS-FTD variants (Strong, 2008; Rascovsky et al., 2011; Snowden et al., 2013). However, it is also appreciated that effective social interactions in everyday life (social cognition), and its consequences (social cognitive deficits) are increasingly apparent in neurodegenerative disorders, including ALS (Elamin et al., 2012).

While most clinical research in ALS has understandably focused on motor pathways, attention is now being directed to all facets of the motor behavior (reflecting ALS as a motor system disorder). Of relevance, mirror neurons and the mirror neuron system (MNS), are special in being active both during motor action and during observation of another individual's motor action, so that the same neuron has motor and sensory representations (Rizzolatti and Craighero, 2004; Keysers and Gazzola, 2006). When observing an action two distinct types of information are obtained – *what* action is being done and, more complex – *what for* or *why?* The 'matching hypothesis' suggests that whenever individuals observe an action being done by someone else, mirror neurons that code for that action are activated in the observer. Since the observers are aware of the outcome of their own motor acts, they also recognize what the other individual is doing without the need for further cognitive processing (Rizzolatti et al., 2009).

While mirror neurons were discovered over 20 years ago, many questions remain regarding their developmental origins and function. Much has been written about a possible role in neurological disorders, but our current knowledge of mirror neurons and the input and output systems to which they belong is still rudimentary, so that it is difficult to predict with any certainty the likely consequences of mirror neuron dysfunction. Nevertheless, given that mirror neurons could be of fundamental importance in the processes of motor control and motor learning, as well as in social cognition (Rizzolatti and Sinigaglia, 2008), it seems worthwhile considering the possible role of mirror neurons in the pathophysiology of ALS. Here we discuss some basic aspects of the MNS and explore how, when disordered, mirror neurons may have relevance in early symptomatology of ALS. In particular we make the case for possible links between mirror neuron function and hand function, gait and articulation, as well as in empathy, all of which are significantly impaired in ALS.

2. Mirror neuron development and function

From an evolutionary point of view, it seems reasonable that there may be some innate mechanisms in place that would be facilitated through sensorimotor learning (Del Giudice et al., 2009). Indeed the MNS might inform the Sapient Paradox (Renfrew, 2008), broadly encapsulated as the 'hardware' for the human neocortex preceding any evidence for higher cognitive outputs by tens of thousands of years. The settling of humans into communities may have been a key factor, in effect the brain being only as productive as those it is shared with, a process in which mirror neurons would be expected to play a crucial role.

While there is no evidence for the existence of a mirror neurons at birth, there is general agreement that infants at birth are attracted to specific sets of stimuli, including faces, their own hands, and especially their own hands in motion (Casile et al., 2011; Ferrari et al., 2013). This may provide sensorimotor experiences that are the necessary scaffolding for mirror neuron development. Empathy, in which mirror neurons have also been implicated (see below), is observable even during the first day of life (Singer, 2006), and infant data using eye-tracking measures suggest that the MNS develops before 12 months of age (Corradini and Antonietti, 2013). In further support, EEG-mu rhythm desynchronization has also been shown in infants during action observation (Virji-Babul et al., 2012).

Such desynchronization, although widely used as an indicator of a functioning MNS, is of course an indirect measure, and cannot prove the existence of populations of mirror neurons that are activated during both action execution and observation, as opposed to separate populations of 'sensory' and 'motor'-related neurons (Braadbaart et al., 2013).

The roles proposed for a MNS include understanding the meaning of behaviors; helping to learn motor tasks or to choose our own actions (Bonini and Ferrari, 2011; Caggiano et al., 2012); and predicting the actions we are observing (Kilner et al., 2007), without assigning a goal to them (Bonini and Ferrari, 2011; Marshall, 2014). It has been suggested that frontoparietal areas provide the basis for bridging the gap between the physical self and others through motor-simulation mechanisms and cortical midline structures engage in processing information about the self and others in more abstract, evaluative terms (Uddin et al., 2007). However, there may exist many classes of mirror neurons, influenced by different aspects of an observed action (e.g., type of the observed motor act, distance of the observer from the observed action, point of view from which the action is observed) (Casile et al., 2011).