The mirror system in human and non-human primates: comparative functional imaging studies

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The existence of mirror neurons in the macaque premotor and parietal cortex, more precisely F5, PFG and AIP, is well established by reports from Parma and other laboratories, and there is plenty of indirect evidence of existence of a similar system in humans (Rizzolatti and Craighero 2004 Ann Rev NS), yet the localization of 'mirror' regions in the human brain remains mysterious. This reflects the basic difficulty, if not impossibility, to compare directly single-cell studies in monkeys with functional magnetic resonance imaging (fMRI) studies in humans. Indeed, monkey cortex is 9.5 times smaller than the human cortical surface (Van Essen et al 2011 Cerebral Cortex), and the behavior of the two species shows marked differences in locomotion, tool use and communication with conspecifics, differences not surprising given that monkeys separated from human lineage more than 23 million years ago. Also the fMRI signals are hemodynamic responses of a completely different nature than neuronal action potentials. Hence, comparing monkey single-cell studies with human fMRI studies is like attempting to solve a single equation with two unknowns. As pointed out 10 years ago (Orban 2002 J Cogn NS) this conundrum can be solved by introducing the missing link: fMRI in the awake monkey (Vanduffel et al 2001 Neuron). fMRI in the anaesthetized monkey (Logothetis et al 1999 Nat NS) does not help as the subjects are alert in the two other types of studies. The strategy which we have developed is to devise an MR paradigm based on known properties of single neurons reported in monkey studies, to validate this MR paradigm in the monkey fMRI and, once validated, to port the paradigm to human subjects. This strategy was used successfully to identify human cortical areas such as MT/V5, phFST or phAIP, which house speed- or disparity-gradient selective neurons, extracting 3D shape form the visual array (Orban 2011 Ann Rev NS). There are several reasons why validation using monkey fMRI is needed: in the area of interest the true proportion of neurons of a given type is often difficult to assess, the response of these neurons to the control stimuli are generally not known, and third, only one or two cortical areas have usually been studied for a given selectivity, leaving it unknown how many other areas house neurons with similar selectivity.

We have shown that in the monkey F5c responds to the observation of grasping action when the actor is visible and not when only the acting hand is visible, while F5a responds in both cases (Nelissen et al 2005, Science). These data obtained initially in the 1.5T, have been confirmed in the 3T (Nelissen et al 2011 J Neurosci). The latter study revealed the circuits originating from the STS and transiting in AIP or PFG, by which the visual action information reaches the premotor F5 neurons. To validate the actor-vs- isolated hand paradigm further, we (Nelissen, Peeters, Vanduffel, Rizzolatti and Orban) generated ‘new stimuli’ in which the acting hand was taken from the whole actor movie, removing low level visual differences and differences in kinematics between the two types of stimuli. By scanning the two types of videos (whole actor, isolated hand) with their controls in the same runs we could directly test which motor areas (F1 to F7, including subparts of F5) had a larger differential visual response for observing the whole actor videos than the isolated hand videos. Only F5c bilaterally showed this interaction. Armed with result we tested the same interactions in human subjects. First we tested the Nelissen et al (2005) stimuli in 20 subjects and observed an interaction in a single frontal cortical site at the level of right ventral premotor cortex. Next we repeated the experiment in 5 subjects using the same stimuli, and replicated the results: a single region of interaction in right premotor cortex. Importantly, the same premotor region showed also the interaction with the ‘new stimuli’. These results strongly suggest that this small region of ventral premotor cortex in the right hemisphere is the human homologue of F5c (phF5c), the home of the mirror neurons. This conclusion is supported by three additional data: 1) the region is located in the most dorsal part of ventral premotor cortex as defined by the DTI study of Tomassini et al
(2007 J Neurosci), 2) it represents hand and mouth actions (Jastorff et al 2010 J Neurophysiol) as does F5c in the monkey and 3) it neighbors a region sensitive to 3D shape from disparity (Georgieva et al 2009 J Neurosci) as it does in the monkey (Joly et al 2009 Neuroimage).

The remaining issue is the right lateralization of the phF5c, which may be related to the hemispheric specialization in humans. Indeed the corresponding region in the left hemisphere reacts little to observation of manipulative mouth actions (Jastorff et al 2010), but does react to intelligible speech. We propose that hypothetically when F5c became connected with a new motor cortical region controlling the larynx (Jurgens et al 1982 Cortex), it adapted its auditory processing (Keysers et al 2002, Science) to become sensitive to the signals generated by this newly evolved and voluntarily controlled larynx. This happened in the left hemisphere because of a preexisting asymmetry for complex sound processing in the monkey auditory system (Joly et al 2011 Cerebral cortex) and the evolutionary pressure to share resources between auditory communication (speech), visual communication (gestures) and observation of manipulative actions.