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CHAPTER 6

General Discussion

6.1 Evidence for mirror neurons in humans

6.1.1 Mirror neuron localization in humans and methodological limitations

Even though mirror properties have been demonstrated using single-cell recordings in several brain regions in monkeys (Cisek and Kalaska, 2004; di Pellegrino et al., 1992; Fogassi et al., 2005; Gallese et al., 1996; Hihara et al., 2015; Keysers et al., 2003; Kohler et al., 2002; Rizzolatti et al., 1996) and humans (Keysers and Gazzola, 2010; Mukamel et al., 2010), what other brain regions might contain mirror neurons remains unclear.

Originally, mirror neurons in monkeys were only described in the anterior inferior parietal lobe and ventral premotor cortices (di Pellegrino et al., 1992; Fogassi et al., 2005; Gallese et al., 1996; Keysers et al., 2003; Kohler et al., 2002; Rizzolatti et al., 1996; Rozzi et al., 2008). Functional magnetic resonance imaging (fMRI) revealed shared voxels, voxels activated during action observation and execution, also in dorsal premotor, supplementary motor cortex, somatosensory cortex and higher visual areas (Caspers et al., 2010; Gazzola and Keysers, 2009). Invasive single-cell recordings in humans are limited to a small group of patients suffering from epilepsy who undergo electrode insertion prior to surgery. This not only restricts the amount of available data sets but also impedes a systematic scanning for neurons with mirror properties as the electrode placements are planned according to medical necessity.

Neuroimaging techniques such as fMRI allow for a brain-wide search for shared voxels. However, the mere existence of shared voxels within one region does not allow inference about the existence of neurons with mirror properties. The spatial resolution of fMRI is limited to a millimeter scale. It is therefore possible that distinct populations of neurons respond to action observation and execution within the same voxel (Gazzola and Keysers, 2009). Therefore, fMRI cannot give direct proof of the existence of mirror neurons, but can help to isolate candidate regions of mirror neuron occurrence.

In Chapter 2 of this thesis, the role of fMRI data acquisition and analysis parameters in the detection of shared voxel regions is investigated. It becomes evident that already during data acquisition past studies have limited their chances to fully describe human shared voxel regions by not covering all sections of the brain, usually neglecting the posterior part of the cerebellum. Interestingly, even if data from this region was acquired, it often got excluded from statistical analysis due to standard bounding box settings during data normalization in the SPM software

package.

Another important analysis choice is the spatial smoothing of data. Smoothing is routinely included in fMRI analysis pipelines to increase the Signal-to-noise ratio. However, smoothing further limits inferences that can be drawn about the occurrence of mirror neurons in a specific region, as spatially distinct neuronal populations processing action observation and populations processing action execution might be blurred into a single voxel (Gazzola and Keysers, 2009). Using unsmoothed data, in Chapter 2 we could replicate the observation of Gazzola and Keysers (2009) that shared voxel regions exist in individual subjects and not only on a group-level. Chapter 2 shows in addition that spatial smoothing can cause the merging of shared voxel regions at the cerebro-cerebellar border, which may have led to an underestimation of the overall number of distinct shared voxel regions. Analysis technique choices, as described in Chapter 2, can further help to understand inconsistencies between meta-analyses on action perception regions in humans (Caspers et al., 2010; Molenberghs et al., 2012; Overwalle et al., 2014).

6.1.2 Evidence for mirror neurons in the human cerebellum

In Chapter 2, we show that more cerebellar regions seem to be involved in action perception than thought previously (Caspers et al., 2010; Molenberghs et al., 2012; Overwalle et al., 2014). This observation is in line with experimental evidence that the processing of action execution and observation are directly coupled. A recent lesion study has shown that synchronic motor execution does not facilitate biological motion recognition following specific cerebellar lesions (Christensen et al., 2014). Studies on motor learning from action observation further highlight a critical involvement of the cerebellum. It is, for example, involved in physical and observational dance motion acquisition (Cross et al., 2009) and has been found to increase activity, along with other regions of the human mirror neuron system, given the explicit intention to learn an observed action (Frey and Gerry, 2006). Similarly, changes in motor cortex excitability were observed following TMS stimulation of the cerebellum during procedural motor learning, regardless of whether the learning was based on actual execution or observational (Torriero et al., 2011).

The theoretical framework for these processes is given by the concept of inverse and forward internal models, which are based on closed-loop interactions between the cerebellum and the cerebral cortex. In short, the forward model estimates the motor and sensory consequences of actions and thereby predicts the outcome of the planned action. The inverse model computes motor commands from a desired state. A interplay of both models may allow for complex behaviors as inferring the

intentions from an observed action or motor learning via error signal estimation (Blakemore et al., 2001; Miall, 2003; Wolpert et al., 1998). The cerebellum has been identified as one of the nodes relevant for these processing streams (Miall, 2003) and the results of Chapter 2 suggest that specific sub-regions of the cerebellum (Lobule VI, VIIb and VIIIa) serve as neural substrate of these processes.

6.1.3 Functional connectivity between cerebellar and cerebral parts of the human mirror neuron system

Chapter 2 provides evidence that different cerebellar seeds show resting state connectivity with distinct regions within the cerebral shared voxel network. This is in line with the notion that different functional roles have been proposed for the superior and inferior posterior regions during action execution and observation (Christensen et al., 2014; Habas et al., 2004). In detail, there are two main streams for processing visually guided limb movements in the cortex. Both circuits start in the posterior parietal cortex (Jeannerod et al., 1995; Tanné-Gariépy et al., 2002), the ventral stream further connects the inferior parietal lobe to the ventral premotor cortex, the dorsal stream connects the superior parietal lobe with the dorsal premotor cortex (Hoshi and Tanji, 2007). On a functional level, it has been shown that virtual lesions to the ventral premotor cortex affect the efficient positioning of the fingers on an object before lifting, whereas virtual lesions to the dorsal premotor cortex affect to timing during the lifting phase (Davare et al., 2006). In this context, Chapter 2 suggests the exciting possibility that the ventral and dorsal visual stream may be coupled to distinct cerebellar regions.

6.1.4 Limitations and future directions

Next to the already mentioned limitations in localizing shared voxel regions using fMRI, several other methodological shortcomings are to be considered. Even though we delivered some evidence that the results of Chapter 2 can be replicated in an independent data set, the impact of different experimental paradigms and stimuli on the detection of shared voxel regions remains unclear. A systematic evaluation of cerebellar responsiveness to different stimuli modalities, for example static versus moving images and familiar versus unfamiliar actions, would be a valuable extension of Chapter 2.

In addition, the action execution task in Chapter 2 was quite unspecific (meaningful object interaction versus rest) and therefore caused wide-spread activation throughout the cerebellum. A more specific execution task would allow a more specific mapping of cerebellar shared voxels, given that several fMRI studies have

indicated a somatotopic organization within the cerebellum (Wiestler et al., 2011), especially when using a field strength of 7T (Stefanescu et al., 2013; van der Zwaag et al., 2013), which allows a better spatial resolution than given by standard 3T MRI scanners.

However, actual evidence for the existence of cerebellar mirror neurons in humans will be challenging. To our knowledge electrodes are not implanted into the cerebellum of epileptic patients, probably due to the fact that the cerebellum does not serve as a source of epileptic seizures. First evidence for cerebellar mirror neurons could however be gathered using single cell recordings in animal studies.

Regarding the functional connectivity between cerebellar and cerebral shared voxel regions, it may be possible to examine whether perturbations of different sub-regions of the cerebellum have distinct impact of processes relying on the ventral and dorsal visual stream, using brain stimulation techniques such as TMS or tDCS.

6.2 Functional role of the mirror neuron system and theory of mind network during action perception

The theory of mind network and the mirror neuron system show limited spatial overlap in the human brain (Overwalle and Baetens, 2009), albeit they are both associated with the processing of the goals and intentions. In the following, evidence for the unique contribution of both networks to action perception are discussed with consideration of the findings in Chapter 3 and 4.

6.2.1 Information processed in the mirror neuron system

It has been suggested that the observation of an action triggers the simulation of this action in our own motor system (Gallese and Goldman, 1998) and thereby enables the processing of the goal of an action (Agnew et al., 2012; Fabbri-Destro et al., 2008; Fogassi et al., 2005; Johnson-Frey et al., 2004; Rosenbaum et al., 2007). Research in non-human primates investigated the role of the inferior parietal lobe (IPL), the analogue of the target region subject to transcranial magnetic stimulation in Chapter 3, on a neuronal level. Single-cell recordings from mirror neurons in the inferior parietal lobe show that firing rates of the neurons are tuned to the overall goal of the action, for example eating versus placing an item

in a container (Bonini et al., 2010; Fogassi et al., 2005). It was also shown that the same neurons responded to the same action executed in a different context (Yamazaki et al., 2010). Some evidence of mirror neuron functioning in the human IPL come from studying fMRI adaptation due to observed and executed actions (Chong et al., 2008).

Chapter 3 shows that the IPL is necessary to determine the goal of an action as well as the mental state of the an actor, when that mental state has to be deduced from the action of the actor. This suggests that the mirror neuron system provides information about motion parameters that are at the basis of different conclusions (goal of action, mental state of actor) that can be drawn from observed actions. However, this does not imply that these conclusions are computed within the mirror neuron system, or mirror neurons themselves. However, the correlation between hesitation processing and analysis of lifting motions observed in Chapter 4 may again indicate a shared underlying process. Whether this shared process is the simulation of actions in the mirror neuron system remains speculative at this point (Gallese and Goldman, 1998).

6.2.2 Information processed in the theory of mind network and stimuli used in theory of mind research

Theory of mind tasks cover a broad array of stimuli that require to change from one owns perspective to the perspective of someone else (person or agent). A recent meta-analysis (Schurz et al., 2014) analyzed neural substrates of different theory of mind task catagories. While three of the task categories (false belief, strategic games and trait judgment) were mostly verbal tasks, the ‘reading-mind-in-eyes’ task uses natural images, the ‘rational actions’ depict actions in comic strips and the ‘social animations’ use animated geometric shapes. The meta-analysis reveals two core regions for theory of mind processing across all catagories: the temporo-parietal junction (TPJ) and media prefrontal cortex (Schurz et al., 2014). This agrees with the notion that, in Chapter 3, the region within the TPJ determined during the functional localizer task (false belief), was also involved in hesitation detection, as shown using transcranial magnetic stimulation. It is noteworthy that natural moving scenes are currently neglected as theory of mind stimuli. This is probably due to the fact that it is hard to develop good control stimuli for natural scenes. However, in Chapter 3 we show that natural scenes can be used to study theory of mind processes by keeping the visual content identical between tasks but alternating task instructions.

6.2.3 Joint information processing

It has been suggested that the mirror neuron system acts as a precursor of mentalizing abilities (Gallese and Goldman, 1998), in the sense that information are transferred from the mirror neuron system to the theory of mind network. This model does not contradict the idea that the goal of an action is processed in the mirror neuron system, whereas the reason behind the action is attributed to the theory of mind network (Rizzolatti and Fogassi, 2014). There is experimental evidence that the mirror neuron circuit works in concert with theory of mind network when socially relevant information are mediated via actions (Agnew et al., 2007; Becchio et al., 2012; Gallese, 2007; Keysers and Gazzola, 2007; Schulte-Rüther et al., 2007), especially when attention is directed towards the intentionality of an action (de Lange et al., 2008).

In Chapter 3, we show that both, the mirror neuron system and the theory of mind network, are necessary to process whether an action was executed hesitantly or not. However, we did not find evidence that the theory of mind network was involved in estimating whether an actor was aiming for a small or large object based on the hand aperture (goal of the action). Given that the visual input was kept constant, we can conclude that attention towards different aspects of the action modulates the activation of and potentially the interaction between the mirror neuron system and theory of mind network.

6.2.4 Early development of perspective-taking skills

It has been argued that perspective-taking is based exclusively on the mirror neuron system in very young children and that skills based on the theory of mind network develop consecutively (Gobbini et al., 2007). Some studies show that the correct attribution of ‘false beliefs’ can only be achieved above the age of 4 years (Gopnik and Wellman, 1992; Ruffman and Perner, 2005; Saxe et al., 2004). However, one has to consider that in many classical false belief tasks, such as the Sally-Anne-task (Wimmer and Perner, 1983), language plays a critical role. It was therefore suggested that the theory-of-mind development happens in two stages: an early non-verbal and a late verbal phase (Hollebrandse et al., 2011; Tager-Flusberg and Joseph, 2005). Some studies indicated that ‘false belief’ processing can be detected already in 15 – 25 month old children using eye-movement parameters in preferential looking paradigms (Onishi and Baillargeon, 2005; Southgate et al., 2007).

In Chapter 4, we present new evidence for correct ‘false belief’ processing in toddlers as young as 24-months. Here, we used an adapted version of the ‘false

belief' preferential looking paradigm by Southgate et al. (2007). In adults, verbal 'false belief' tasks activate the so-called theory of mind network (see: functional localizer task in Chapter 3). Chapter 4 provides some evidence that 24-month-olds process mental states (uncertainty) while observing a hesitant hand movement. In adults, response latencies during hesitation detection correlate with self-reported perspective taking skills and depends on both, the mirror neuron system and theory of mind network, as demonstrated using transcranial magnetic stimulation in Chapter 3. Considering both findings, there is evidence that the development of perspective-taking skills may happen earlier than thought previously and may rely on different neural substrates (i.e. mirror neuron system, theory of mind network), depending on the given task.

However, the findings of Chapter 4 give no direct proof about the brain networks involved in perspective-taking based on story-lines or action observation in toddlers. As advocated by Mahy (2014), closer interaction between developmental psychology and neuroimaging is necessary to link the questions of how and where mental states are processed during development (Mahy et al., 2014). For example, there is evidence that the activation of the right temporo-parietal junction becomes more reliable and specific during mental state processing between ages 5 and 11 (Gweon et al., 2013; Kobayashi and Temple, 2007; Saxe, 2009).

6.2.5 Limitations and future directions

The actual biological mechanisms, neural substrates and timing of the interaction of the mirror neuron system and theory of mind network go beyond the scope of this thesis, but are an exciting field for future research. This is particularly true since recent research suggests that the information processing between both networks might be deficient and thereby potentially contributes to social deficits in autism spectrum disorder (Fishman et al., 2014; Libero et al., 2014).

In terms of techniques, some limitations need to be considered for the rTMS experiment. In Chapter 3, an effect of rTMS was shown on response latencies but not on task performance. It is possible that the number of repetitions, limited by the rTMS effect duration, impeded the detection of a performance decrease. A replication of the current results using recently developed, more powerful stimulation techniques like theta-burst stimulation (Huang et al., 2005) would help to increase confidence in the findings of Chapter 3.

It may further be noted that the results of Chapter 3 do not allow direct inference on whether the inferior parietal lobe and temporo-parietal junction themselves are critical for hesitation processing. It has been shown that repetitive TMS

spreads along task-based (Shafi et al., 2013; Valchev et al., 2016) and resting-state functional networks (van der Werf et al., 2010). It is therefore possible that not the stimulation of IPL and TPJ, but of a functionally connected node (of the mirror neuron system or theory of mind network) evoked the observed changes in behavior.

In Chapter 3 we show that gestural hesitation is a good model to study the interaction of the mirror neuron system and theory of mind network. Today, there are only a limited number of stimuli available that evoke the joint activation of both networks (Overwalle and Baetens, 2009). Chapter 5 delivers some additional evidence that gestural hesitation might also be a useful modality to study action perception during development. For current limitations and possible future improvements of the stimuli, please refer to Chapter 4.

6.3 Action perception and social functioning

Autism spectrum disorder (ASD) is a developmental disorder, that is considered highly heritable and thought to manifest early during development. Already two-year-old children diagnosed with ASD orient preferentially towards displays of light and sound rather than point-light animations showing human movements (Klin et al., 2009). Another study showed, that about 40% of children with autism preferred moving geometric patterns over videos of dancing children at age one to three (Pierce et al., 2011). One explanation is an innate deficit in the processing of actions and biological motion. In their review, Gowen and Hamilton interpret atypical findings in coherent motion and biological motion thresholds in autism spectrum disorder as impairments in sensory signal integration (Gowen and Hamilton, 2013). This early processing deficits may help to explain why children with autism spectrum disorder have difficulties to interpret social situations and still experience such difficulties during adulthood (Szatmari et al., 1989; Venter et al., 1992).

However, there is evidence that performance differences on biological motion tasks are more pronounced in children than in adults diagnosed with ASD (Kaiser et al., 2010; Kaiser and Pelphrey, 2012; McKay et al., 2012). This observation raises the question whether compensatory mechanisms improve action perception with age (Kaiser et al., 2010; McKay et al., 2012). On the other hand, it may be possible that the instruction to attend to the biological motion stimuli, lead to an enhanced processing in the adults with ASD, which does not reflect action perception in real-life. In Chapter 5, we show that a neurotypical activation of

the action perception regions does also occur in adults with ASD when attention to the stimuli is neither instructed nor necessary to perform the given task. An increased activation in the lateral occipito-temporal cortex, in adults with ASD compared to a control group, may be an indication of a compensatory mechanism that boosts perception of actions in adults with ASD.

Interestingly, a study by Jones and Klin (2013) challenges the concept of innate deficits and late compensatory mechanisms. It shows that children, who later receive a diagnosis of ASD, did not show any deficit in eye gaze to social stimuli before the age of 2 to 6 months (Jones and Klin, 2013). They conclude that the social deficits that manifest later in life may be caused by social avoidance mechanisms. Thus, the increased brain activation found in Chapter 5 could also be interpreted as additional attentional effort, which counteracts the acquired avoidance behavior towards biological actions, even more so in a research environment. This alternative explanation cannot be dismissed, even though some aspects of attention were accounted for in Chapter 5.

Future research should be targeted at a systematic assessment of action processing in ASD (task instruction, social context) including measurements of avoidance behavior (eye gaze recording) and arousal (heart rate, skin conductance). Ideally, longitudinal studies would help to characterize the changes in action perception across different age groups.

6.4 The impact of stimuli and analysis methods

This thesis investigated some aspects of neural correlates of action perception. Next to presenting some new and some confirmative findings of previous research, this thesis is also intended to raise some awareness of methodological practice. One example is the usage of recorded real-life movements to study the mirror neuron and theory of mind network. Chapter 3 shows, that using movies of actions instead of vignettes or verbal materials seems to change the way that the putative mirror neuron system and the theory of mind network interact. This shows, as previously argued by Keysers and Gazzola, 2007, that the apparent dissociation of pMNS and ToM networks is actually an artifact of using distinct stimuli to study the two networks, whilst crafting naturalistic stimuli that can be used to perceive action goals and mental states can qualify this picture by evidencing the opportunities for the two networks to interact. Another aspect that deserves attention in future research is the careful consideration of analysis parameters when evaluating fMRI results in the cerebellum. Although the neuroimaging community has converged to

use a set of rather standard analysis methods, including default bounding boxes and smoothing of 2–3× the voxel size, Chapter 2 shows how important it is to critically investigate whether such standard settings are appropriate in all cases, as we show that such methods actually occlude one’s ability to detect the cerebellar contribution to specific functions such as action observation.