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Neural correlates of action perception

Suttrup, J.

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CHAPTER 1

General Introduction

1.1 Scope of the thesis

Understanding a person's intentions can be highly complex, but is of utter importance for social interaction. For example, a person might pick up a knife to cut vegetables or to throw it at someone. While observing the scene, the intention we assign to this person has a crucial influence on how we choose to react. Ideally, the person's intention should already be deduced as the person reaches for the knife, in order to maximize the time to choose an appropriate response. So how is it possible to decipher a person's intention purely via observation of a hand movement?

Our current understanding of action observation is strongly influenced by the description of mirror neurons in the 1990's (di Pellegrino et al., 1992). Mirror neurons are motor neurons that respond during the execution of specific actions and also respond while observing the same action. In other words, a simulation of the action is run in our own motor repertoire. Intriguingly, for a large proportion of mirror neurons the common activation during action execution and observation can only be observed if the goal of the action is the same for both modalities. The goal behind an action seems – at least partly – to be decoded in the motor system itself, opposed to an exclusive processing of the goal as an abstract concept in higher cognitive brain regions.

The simplicity of this theory is very appealing. However, a lot of questions remain unanswered. Single-cells recordings (Mukamel et al., 2010) and functional magnetic resonance imaging in humans (for a meta-analysis see: Molenberghs et al., 2012) suggest that neurons located outside of the classical motor regions show mirror properties. The number of brain regions which contain mirror neurons and their region-specific functions remain unclear. One region is of specific interest when it comes to the localization of mirror neurons, but at the same time often outside of the scope of the mirror-neuron literature: the cerebellum.

The cerebellum is a key region for motion execution specifically in terms of processing prediction errors and has been shown to also play a role during action observation (Schlerf et al., 2014). Action prediction on the other hand is one of the key functions attributed to the mirror neuron system and it has been suggested that the cerebral mirror neuron system and the cerebellum form a loop within the action prediction circuit (Miall, 2003). However, the mirror neuron properties within the cerebellum are difficult to define as the quality of measurements within the cerebellum are frequently sacrificed in favor of cerebral structures in neuroimaging studies. Therefore, the first goal of this thesis is to use fMRI to localize subregions within the cerebellum that potentially contain mirror neurons using data acquisition

and analysis pipelines that are optimized for activation in cerebellar structures (Chapter 2). These findings can inform later neurophysiological studies about cerebellar candidate regions to perform confirmative single cell recordings.

It is also debatable whether the mirror neuron system is sufficient to fully understand the intention behind an action (Herschbach, 2011). Another system involved in mentalizing is the theory of mind network. The mirror neuron system and theory of mind network have little spatial overlap and their interaction is poorly understood (Overwalle and Baetens, 2009). However, their interaction becomes very relevant when an observed action does not only imply an intention but also a mental state, for example uncertainty. A second goal of this thesis is thus to investigate which kind of information about mental states conveyed by motion are processing in which network using transcranial magnetic stimulation (Chapter 3). Subsequently, the following question arises: How does the processing and understanding of action develop and what role to both networks play during ontogenesis. This question inspired the study presented in Chapter 4, which probes action understanding in toddlers using eye-tracking.

Finally, as mentioned in the beginning, action observation and social functioning are causally linked. Does this imply that social impairments can be based on impairments in action observation? For example, Autism Spectrum Disorder (ASD) is characterized by difficulties in social communication and interaction. Intriguingly, several studies support the theory that perception of movements seems to be altered in ASD (for a review see: Kaiser et al., 2012). Therefore, a final goal of this thesis is to investigate whether neural responses during movement perception are altered in ASD, even when there was no explicit instruction to observe the motion, like it usually happens in daily life (Chapter 5).

1.2 Research methods

This short introduction reveals that we are a long way from grasping the seemingly simple process of observing and understanding an action. The following paragraphs describe the techniques that were applied in the context of this thesis.

1.2.1 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a technique to visualize anatomical brain structures and functional processes using a strong magnetic field. Over the past decades, MRI has become the gold standard imaging technique (Cui et al., 2011). Functional magnetic resonance imaging (fMRI) monitors changes of the blood

oxygenation level dependent (BOLD) signal. The BOLD signal strength is strongly dependent on blood flow and blood oxygenation and is therefore used as an indirect measure of neuronal activity within specific brain regions (Logothetis, 2002). The main limitation of MRI compared to techniques as electroencephalography is its poor temporal resolution. A BOLD response towards one stimuli is estimated to have a delay of several seconds (Magri et al., 2012). The MRI scanners used during data collection for this thesis had a field strength of 3 Tesla, a common standard in the brain imaging literature. This allows a spatial resolution of about $3 \times 3 \times 3$ mm (size of one resolution element, so-called voxel).

Functional MRI data also allow inferences about functional connectivity between brain regions. One example is the resting state connectivity, which can be measured in the absense of a task or stimulus. Resting state connectivity allows inference about regions that typically coactivated together (Hampson et al., 2002). In the context of this thesis, resting state connectivity maps are used to demonstrate that cerebellar regions activated during action observation and execution preferably communicate with cerebral regions activated by the same tasks, another lead about the existance of cerebellar mirror neurons.

1.2.2 Repetitive transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a technique that allows the stimulation and modulation of neurons via electromagnetic induction of an electric field in the brain (Rossi et al., 2009). TMS can be applied as single-pulse stimulations or in form of repetitive trains of stimulations (rTMS). Repetitive TMS induces long-lasting effects on neuronal excitability (Hoogendam et al., 2010). Changes in excitability are most likely caused by neuronal mechanisms resembling long-term potentiation or long-term depression combined with metaplasticity effects (Hoogendam et al., 2010). The direction of stimulation (inhibitory or facilitating) depends on the choice of TMS parameters (frequency, intensity, duration). The most reliable parameter combination to induce inhibitory effects is 1 Hz frequency at an intensity equal to 90% of the passive motor threshold (Hoogendam et al., 2010). It has been shown that the inhibitory effect duration is proportional to the stimulation duration (Rossi et al., 2009). For example, 15 minutes of stimulation creates an inhibitory effect at the site of stimulation that lasts for about 7.5 minutes. One advantage of this technique is that 1 Hz rTMS can be applied offline, before the beginning of the experimental task. Therefore, the participants are not distracted by tactile or auditory TMS-induced sensations during the task.

In the context of this thesis, inhibitory 1Hz TMS is used to learn what information

are processed in two different brain networks (MNS, ToM network) engaged by the same stimuli. These inferences can be made by monitoring task performance over different task (by making different aspects of the stimuli task-relevant) while altering the processing in different brain areas. In other words, if we hypothesize that the activity of an area of interest is essential for behaviour, we would expect that a perturbation of that activity via TMS will be manifested in the behaviour.

A limitation of TMS is that it remains unclear how the electric field spreads in the brain after TMS stimulation (Bolognini and Ro, 2010). A risk of stimulation spreading into adjacent brain regions is most likely at high frequencies (20–25 Hz) and high intensities (110%–130%) (Rossi et al., 2009) and therefore less relevant for the 1 Hz stimulation described in Chapter 3. Importantly, electric field spread across functional networks has been demonstrated using high-definition electroencephalography recordings (Ilmoniemi et al., 1997). Thus, interference with one node of a network can tentatively be regarded to as network interference. This property of TMS allows us to make inferences about the role of the MNS and ToM network during action observation.

1.2.3 Eye-tracking

Eye-tracking is a technique to record the eye gaze of a participant during an experiment. The eye-tracking system hardware consists of an infra-red camera and an infra-red diode. The camera records the eye movement of the participant. The infra-red diode is used to enhance the automated detection of the pupil by the eye-tracking software and evokes a reflection from the cornea, which is also used for determining the position of the eyes. After calibration, the relative position of the pupil and corneal reflection can be converted to the eye gaze of the participant on the target screen. The eye gaze translates into a pattern of fixations and saccades.

Eye gaze can be used to simply monitor a participants attention to a stimuli (as used in Chapter 5). In the context of action observation, eye gaze is frequently used to study how a participant predicts the outcome of an action. It has been repeatedly shown that toddlers move there eye-gaze to a location where they expect at action to happen or an object to appear next (Onishi and Baillargeon, 2005; Southgate et al., 2007; Tummeltshammer et al., 2014). Importantly, eye-tracking enables researchers to gather information about cognitive processes without explicit task instructions or the need for verbal feedback (Scheiter and van Gog, 2009). It is therefore a valuable tool for developmental research, for example to investigate how toddler understand mental states conveyed in actions before they can phrase their observations verbally (Chapter 4).

1.3 Relevant brain networks

Viewing the brain as an accumulation of segregated networks is rather outdated, especially since the emergence of advanced structural and functional connectivity analyses. Nevertheless, some networks relevant in the context of this thesis are highlighted below.

1.3.1 Action observation network

The action observation network (AON) is activated when we observe goal-driven movements. In functional imaging experiments, it can robustly be mapped when contrasting the observation of videos showing real-life actions, for example picking up a knife and cutting a slice of bread from a loaf, with a series of meaningless hand movements, for example a hand moving back and forth over a table (Arnstein et al., 2011; Gazzola and Keysers, 2009).

The exact composition of activated brain regions depends on the stimuli presented. However, the major clusters of activation are usually found bilaterally in the premotor regions, primary and secondary somatosensory cortex, inferior parietal lobe, the fusiform gyrus and higher visual cortices, especially the motion-sensitive area V5 (for a meta-analysis see: Caspers et al., 2010, Molenberghs et al, 2012).

1.3.2 Mirror neuron system / Shared voxel network

As mentioned before, mirror neurons are neurons responding to the execution and observation of certain goal-driven actions. They were first described in the premotor and parietal cortex of macaque monkeys using single-cell recordings (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). Their dual responsiveness suggests a potential role of mirror neurons in action observation, action understanding, motor learning and imitation. Soon it was speculated whether mirror neurons can be found in the human cortex. The first direct measurement of neurons with mirror properties was executed using single-cell recordings from electrodes implanted in candidates for surgical treatment of epilepsy (Mukamel et al., 2010).

Electrodes implanted for medical evaluation offer the unique opportunity to record responses from individual human neurons. However this technique has an important limitation: the implanted brain regions are chosen for medical reasons and a systematic search for mirror neurons across the cortex is therefore impossible.

Thus, the spatial distribution of mirror neurons remains unclear.

Imaging studies define the network of brain regions that is activated during action observation and action execution as the human mirror neuron system (hMNS). Practically, this usually requires a localizer task for the AON network, which is subsequently masked with the activation map of an action execution task. It classically includes the dorsal and ventral premotor cortex, primary somatosensory cortex, inferior parietal cortex and the motion-sensitive visual area V5 (for a meta-analysis see: Molenberghs et al., 2012). However, additional regions such as the cerebellum have been suggested to show vicarious activations (Gazzola and Keysers, 2009).

The term mirror neuron system should be handled with care. Firstly, only about 10% of neurons in the premotor cortex of macaques show mirror properties (Kilner and Lemon, 2013). Secondly, the spatial resolution of fMRI is limited. Voxels that are active during action observation and execution may contain neurons with mirror properties but may also contain sub-regions with neurons merely responding to either observations or execution (for a detailed discussion see: Gazzola and Keysers, 2009). Therefore, the term shared voxel network is frequently used to substitute the term mirror neuron system in this thesis.

1.3.3 Biological motion network

The biological motion network is closely related to the action observation network, although they are often treated as two independent entities in the literature. The two networks show substantial spatial overlap, for example in higher visual regions (V5), inferior parietal regions and premotor cortex (see Chapter 2 and Chapter 5). The naming of the networks largely depends the stimuli utilized. While the action observation network is usually connected to hand, foot or mouth movements, the biological motion network is often described in the context of whole-body movements. The observation of whole-body actions is more likely to evoke strong responses in the extrastriate body area (EBA), fusiform body area and superior temporal sulcus (for a review see: Peelen and Downing, 2007). Furthermore, the action observation network typically describes brain activations in response to real-life video or picture stimuli. The biological motion network is often based on so-called point-light displays (PLD). In PLDs, the visual representation of a human's movement is reduced to a set of dots representing the joints and head. Humans are remarkably good at identifying the type of motion and even emotions and the gender conveyed in a PLD (Alaerts et al., 2011). The minimalistic representation of a motion enables researchers to study certain aspects of motion, for example

velocity profiles, using randomly moving dots as an excellent control condition for visual input (Johansson, 1973). Thus, PLDs are a popular approach to study biological motion, which is characterized by a typical pattern of accelerations and decelerations. Therefore, these stimuli are ideal to study differences in brain activation during motion processing between participants with ASD and control participants (Chapter 5) as the motions is not obstructed by other social stimuli (faces, gender, body language)

1.3.4 Theory of mind network

Theory of mind (ToM) describes the awareness that a person can have a belief that is different from one's own belief and/or different from reality (Premack and Woodruff, 1978). The ToM ability develops during infancy and is thought to co-develop with language skills. Therefore, it is highly interesting to study the co-development of theory of mind and action understanding skills in toddlers (Chapter 4). Theory of mind skills are often tested using a so-called false belief task. A false belief task typically features two actors and one object. During a temporary absence of the first actor, the second actor moves the object from one occluded location to another. If ToM skills are fully developed the participant will expect the returning first actor to look for the object in the original and not in the current location. A false belief task can be visual or verbal. In a broader sense theory of mind can be described as thinking about another person's mental state.

Imaging experiments using ToM tasks typically report increased activation in a bilateral network, consisting of the temporo-parietal junction, superior temporal sulcus, temporal pole, ventral prefrontal cortex, inferior frontal gyrus and precuneus (for a meta-analysis see: Bzdok et al., 2012). Importantly, there is very little spatial overlap between the mirror neuron system and theory of mind network (Overwalle and Baetens, 2009), which leads to the question under which circumstances information about goals and mental states are processed in either network (see Chapter 3).

1.4 Autism spectrum disorder

Autism spectrum disorder (ASD) is a developmental disorder that manifests in social interaction and communication deficits as well as repetitive behaviors. It is considered persistent throughout life. A clinical diagnosis is based on questionnaires and interviews with the individual suspected of having Autism Spectrum Disorder and, if possible, parents and/or caregivers. ASD is a highly heritable disorder, with

genetic heritability estimated to lie between 56% and 95% (Colvert et al., 2015).

As indicated by the name, the diagnosis ASD comprises a whole spectrum of disorders showing somewhat consistent phenotypes. The newest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) abandoned the subdivision into autism, Asperger's Syndrome and pervasive developmental disorder not otherwise specified (PDD-NOS), as these classifications could not be sufficiently supported by scientific evidence. So-called high-functioning autism (HFA) is not a clinical classification, but merely indicates that individuals do not suffer from mental retardation, having an IQ of above 80. This population is very valuable for scientific research: high-functioning autism offers a unique opportunity to study different aspects of the social brain and its neuronal substrates, because in high-functioning autism social cognition is rather selectively impaired, while non-social cognitive functions remain generally at a neuro-typical level. In Chapter 5 of this thesis, the unique features of this population

1.5 Thesis outlook

Here I briefly describe which chapters are addressing the study goals stated in this introduction. Chapter 2 will explore the distribution of shared voxel regions within the cerebellum using functional magnetic imaging. Different processing pipelines are used to optimize the detection of cerebellar activations. A comparison of these pipelines is used to explain inconsistent literature reports of cerebellar shared voxel regions. A functional connectivity atlas is used to estimate the connectivity between cerebral and cerebellar shared voxel regions.

Chapter 3 explores the role of the shared voxel network and theory of mind network during action observation. Activations in nodes of both networks are modulated using transcranial magnetic stimulation. These disturbances allow us to approach the following questions: Are both network necessary to anticipate the goal of an action efficiently? And what impact does the TMS stimulation have if the participant needs to deduce a mental state just by observing an action?

Chapter 4 explores the concurrent development of goal detection and mental state attribution during infancy. Using eye-tracking in two-year-olds, we investigate how much information about an action toddlers deduce during action observation. For this experiment, we are using an adapted version of the stimuli used in Chapter 3.

Chapter 5 explores if motion processing, specifically biological motion processing, is altered in individuals diagnosed with Autism Spectrum Disorder. An alteration

may indicate that a difference in processing movements can be one factor leading to difficulties in social interaction, emphasizing the relevance of studying action observation in neuroscience.

Finally, Chapter 6 includes a general discussion, which demonstrates how the findings presented in this thesis aid our understanding of the processing of movements, in terms of insight into the potential spatial location of cerebellar mirror neurons, the nature of information processed in the MNS and ToM network during action perception, the challenges of studying movement-based mental state deduction in toddlers and the association between spontaneous motion processing and social functioning in ASD.