Aus der Neurologischen Universitätsklinik Tübingen
Abteilung Kognitive Neurologie

A Frontoparietal Network for Cognitive Control of Gaze Following

Inaugural-Dissertation
zur Erlangung des Doktorgrades
der Medizin

der Medizinischen Fakultät
der Eberhard Karls Universität
zu Tübingen

vorgelegt von

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2022

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Tag der Disputation: 18.01.2022

to my dear ones
an endless source of love and support

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List of Abbreviations

ACC	anterior cingulate cortex
ADS	attention deficit disorder
ADHS	attention deficit hyperactivity disorder
ANOVA	analysis of variance
ASD	autism spectrum disorder
BA	Brodmann area
BOLD	blood oxygen level dependent
CBF	cerebral blood flow
CBV	cerebral blood volume
CO	cingulo-opercula
DAD	direction of attention director
dlPFC	dorsolateral prefrontal cortex
EDD	eye direction detector
EEG	electroencephalography
ERN	error related negativity
ERP	event related potential
FDR	false discovery rate
FEF	frontal eye field
FP	frontoparietal
fMRI	functional magnetic resonance imaging
FWHM	full-width half-maximum
GFP	gaze following patch
GLM	general linear model
ID	intentional detector
INS	insula
IPS	intraparietal sulcus
LFP	local field potential
MFC	medial frontal cortex
MNI	Montreal Neurological Institute
MT	middle temporal area
MTG	middle temporal gyrus
MUA	mutual activity
OFC	orbitofrontal cortex
PCC	posterior cingulate cortex
PET	positron emission tomography
PFC	prefrontal cortex
POR	primitive orienting reflex
PPC	posterior parietal cortex
pSTS	posterior superior temporal sulcus
RCZ	rostral cingulate zone
ROI	region of interest
SAM	shared attention mechanism
SMA	supplementary motor area
SPM	statistical parametric mapping
STS	superior temporal sulcus
ToM	theory of mind
ToMM	theory of mind mechanism
vlPFC	ventrolateral prefrontal cortex

1. Introduction

1.1. The ‘Mindreading System’ and its Neural Correlates

1.1.1. Gaze Following

The eyes are considered to be the most important component of a face and play an important role in all primate facial expressions (Andrew, 1963). The eyes can reveal information about one’s mental as well as emotional state, one’s thoughts and desires. In humans they are an essential part of nonverbal communication. Already infants at the age of 2 months spend considerably more time focusing on the eyes of a counterpart than additional features of the face (Maurer, 1985), suggesting that humans, as well as non-human primates (see below), developed a complex communication system based on information contained within the eyes (Emery, 2000). The pure morphology of a primate’s face helps to highlight this region even more. Eyebrows and high cheekbones surrounding the area involuntarily lead the observer’s attention to the eyes (Emery, 2000). Additionally, the dark iris compared to the bright sclera in humans enables observers to extract additional information by discriminating the direction of gaze even from some distance (Kobayashi and Kohshima, 1997).

To determine were an individual’s attention is directed, besides the direction of the gaze, primates rely on additional hints: the direction of the head as well as the direction of the body. But still, these cues are arranged in a hierarchy, where eye gaze is considered to provide the most important information (Perret et al., 1992). The directional information of eye gaze can be used to follow the person’s gaze and direct one’s own attention in the same direction, even onto the same object. This is called joint attention.

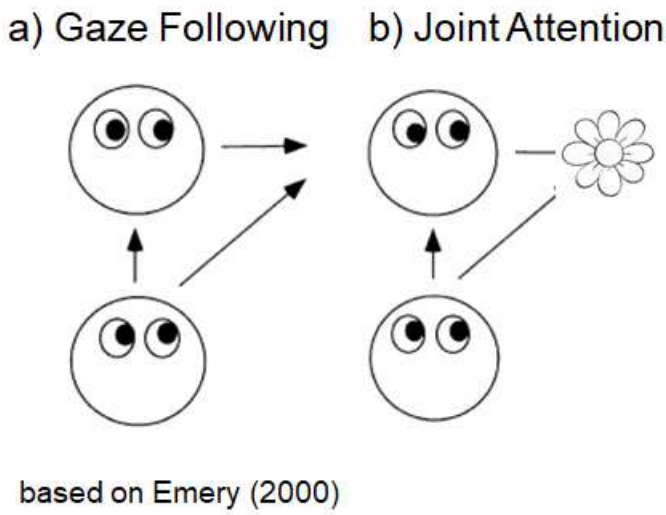

Figure 1: Gaze Cues
a) Gaze Following is when one recognizes that the counterpart is looking somewhere in
space and follows the line of sight
b) Joint Attention is when one not only follows the gaze of a counterpart, but also shifts
the own focus of attention to the same object in space

The age at which human infants start to perform gaze following is controversially discussed and ranges between 3-18 months (Emery, 2000). Gaze following is reliably established within the age of 10-12 months (Corkum and Moore, 1998). In the beginning, infants follow their mothers gaze without redirecting their focus of attention, but at around the age of 18 months are even able to direct their attention to objects outside their visual field, for example behind them (Butterworth and Jerrett, 1991). In infants gaze following is not only considered to be essential for observatory learning (Mineka et al., 1984) but also for early stages of learning a language (Dunham et al., 1993; Munday and Gomes, 1998). Associating a word with the presence of an object can only be achieved when paying attention to this specific object. This requires establishing joint attention by extracting another's direction of attention and shifting one's own focus of attention to the same object. Liuzza et al. (2011) were able to show that there is also a large social relevance in gaze following, since humans tend to more often to follow the gaze when they are emotionally close.

Tracking down a specific object in space by following the gaze of another person is very precise. Butterwoorth and Jarrett (1991) claim that humans perform gaze following in a geometric way, rather than simply using the directional information and follow that direction until an object of interest would come into sight. Geometrical gaze following is based on a gaze vector of precise direction and length, specifically indicating the correct object. Bock et al. (2008) performed an experiment where subjects had to judge which object, singled out of an array of identical objects, a sender was gazing at. Subjects located the correct target precisely and even various ways of manipulation could not diminish the accuracy of gaze following, preconditioned both eyes of the sender were visible.

Several studies in humans (Friesen and Kingston, 1998; Driver et al., 1999; Langton and Bruce, 1999) showed that observing head and eye gaze directions leads to early, reflexive shifts of attention. Langdon and Bruce (1999) presented letters appearing in the periphery of the visual filed, equally often in all 4 locations (up, down, left, right). Before this a head was presented in the center of the visual field, randomly directing in one of those four directions but not cueing where the next letter might appear. Although subjects were instructed to ignore this spatial information of the head, nevertheless targets were detected faster, when they were cued by the head orientation before. These reflexive shifts of attention could not be triggered by non-social directional cues like arrows (Jonides, 1981), which underlines the unique mechanisms of gaze following.

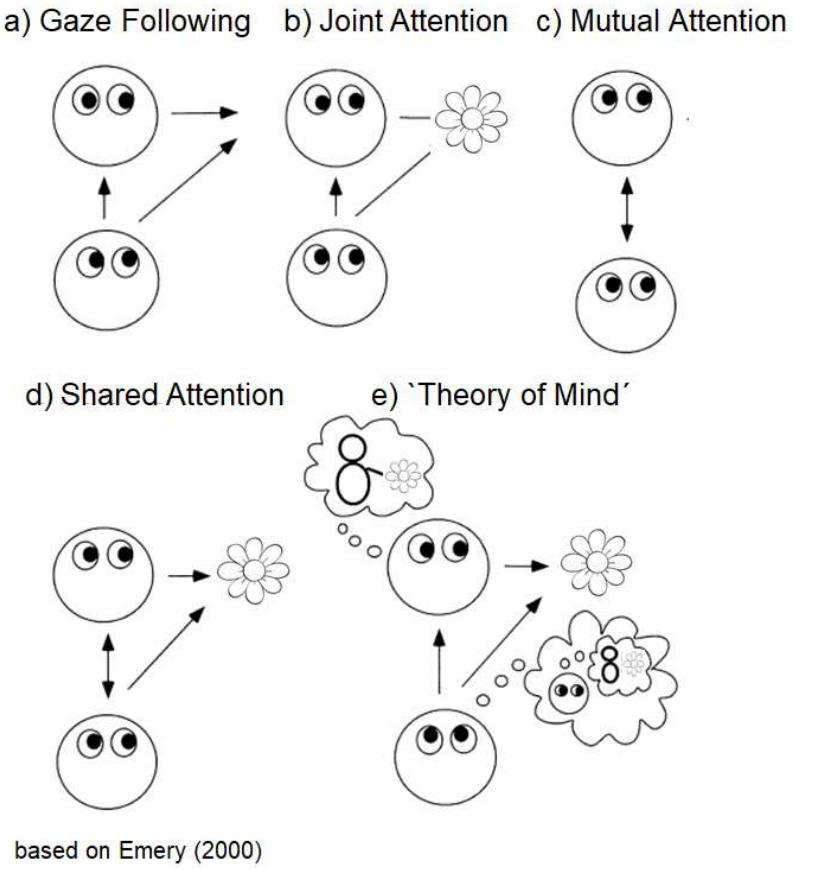

Figure 2: Social Cognition
a) and b) see above
c) Mutual Attention is when two counterparts are focusing on each other
d) Shared Attention is when the focus of attention is on each other (mutual attention), as well as on the same object (joint attention)
e) Theory of Mind is when one creates a hypothesis of the internal intention of the counterpart regarding the object of attention

Gaze following is the essential and indispensable basis to creating a Theory of Mind (ToM). Gaze following enables human beings to follow someone's gaze to an object in space and by shifting the own focus of attention to the same object, one can establish what is called joint attention. If one is not only focusing on the same object, joint attention, but also focusing on the counterpart, what is called mutual attention, a dyadic interaction in which the two agents attend to each other, one establishes shared attention. Shared attention is characterized by the combination of these two complementary aspects of attention. Inferring that paying attention to an object does reveal information about the thoughts, needs and desires of the observer, one can finally create a Theory of his/her Mind

(ToM). By projecting one's own desires, beliefs and concerns associated with the object of shared attention onto the other, the observer constructs a presumption of the other's mind, a presumption that is further elaborated by additional information on the other's emotional state, i.e. provided by facial or gestural expressions. Therefore aspects like empathy and one's own experiences are essential requirements to create a sufficient hypothesis (Emery, 2000) (Figure 2).

In 1994 and 1995b Baron-Cohen proposed a modular system for a Theory of Mind, where the eyes were considered to play the central and most important role. He called the eyes being the best 'window to the mind'. His model is consisting of an Eye Direction Detector (EDD) – representing Gaze Following and Joint Attention - , an Intentional Detector (ID), a Shared Attention Mechanism (SAM) and a Theory of Mind Mechanism (ToMM) (Figure 3).

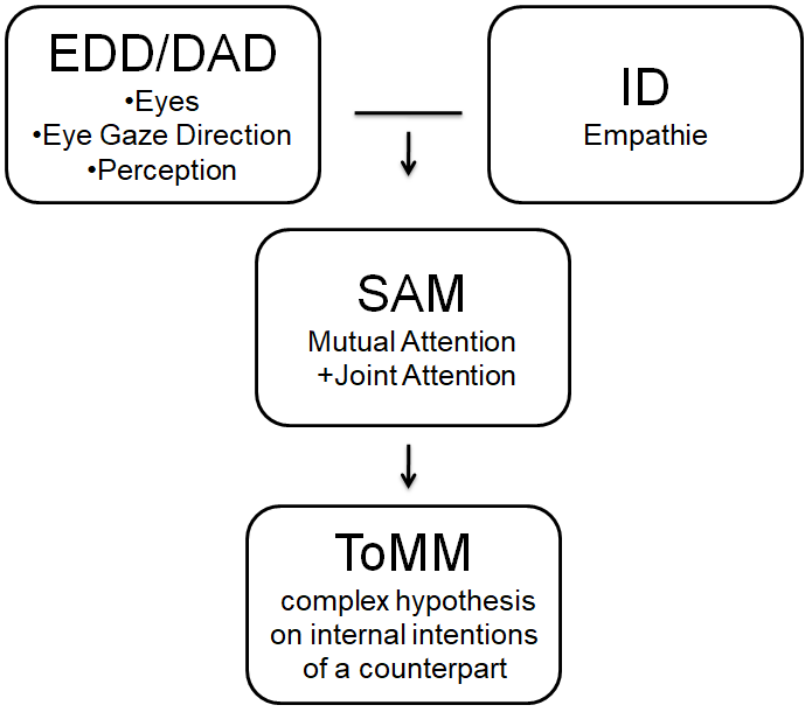

Figure 3: Modular System of Social Cognition
EDD: Eye Direction Detector; ID: Intentional Detector;
SAM: Shared Attention Mechanism; ToMM: Theory of Mind Mechanism.

The EDD has three functions: first to ensure the presence of the eyes as stimuli, second to detect the eye gaze direction and third to assume that the counterpart is actually 'seeing' and perceiving what her/ his eye gaze is directed at.
The ID is considered to be a primitive perceptual mechanism that attributes desires and goals to the other based on one's own experience and empathy as well.
Those two are necessary to create the SAM. The SAM consists of two functional components. The first one is the ability to deploy mutual attention, an ability that develops in infants between 9-18 months of age. The second component that makes up the SAM is the ability to establish joined attention.
The ToMM is a quite complex module. According to Baron-Cohen it has two major functions: First it is capable of all aspects of mental states in humans, including pretending, believing and knowing. Secondly based on this knowledge it would set up a theory on what others are going to do next and why they are behaving that way.

Non-human primates also show a preference to focus on the eyes of a conspecific's face. When pictures of primates are presented to rhesus monkeys, they spent most of the time observing the other's eyes and the region around (Keating and Keating, 1982). As well as humans, monkeys are also influenced by facial expressions and eye gaze. Furthermore, monkeys tend to more often follow the gaze of animals that adopt a high position within their hierarchy (Shepherd et al., 2006). Monkeys are also very precise in tracking down the specific object in space by following the gaze of a conspecific. Tomasello et al. (1999) showed that primates also perform gaze following in a geometric way rather than just following directional cues. In the experiment chimpanzees continued to follow the gaze to the correct target whilst ignoring distracting objects located in the same direction. Marciniak et al. (2015) demonstrated that gaze following in rhesus monkeys involves an early, insuppressible shift of attention, caused by head gaze. In general, gaze following in human and non-human primates share many features such as swiftness, a lack of full cognitive control and an influence by additional social cues. On the other hand, monkeys

may not understand that they actually share attention and they most probably lack the ability to create a Theory of the other's Mind (Emery et al. (1997).

Studies of people suffering from autism spectrum disorder (ASD), a disease that is characterized by disturbed social interactions, point towards a disturbance of the mechanism to process the other's gaze. For instance, ASD subjects may exhibit disturbances of sustained eye contact (Kanner, 1943), gaze following (Leekham et al., 1998) and the deployment of joint attention (Charman et al., 1997) and may therefore be unable to develop a viable ToM (Baron-Cohen et al., 1995a). However, Baron-Cohen et al. (1995a) were able to show that autistic children may very well be able to track down the direction of gaze of a counter-part, when asked which object a sender is looking at, yet, are unable to use this information to develop a Theory of his/her Mind. This inability is probably due to deficits in empathy and taking in a third person perspective, symptoms associated with ASD. This conclusion is based on experiments in which the group presented a smiley face to autistic children. They were able to distinguish whether the smiley was looking at them or not and if, alternatively, the smiley was looking at one out of four candies. Yet, when asked which candy the smiley might probably ask for, they could not provide an answer.

1.1.2. The STS Region

There is a region located in the superior temporal sulcus (STS) region that is selectively sensitive to the perception of eyes, faces and bodies (Allison et al., 2000).
Several studies in monkeys have reported on neuronal activity in the STS that is related to the perception of body parts and body movements. Hasselmo et al. (1989) detected single cell activity in the lower bank of the STS region evoked by head movements and Perrett et al. (1989) showed that cells in the lower bank of the STS region respond not only to hand movements, but also that cells fired more strongly, when the movement was goal directed.
Perrett and Emery (1994) claimed that neurons in the STS might extract information for redirecting attention, using a variety of cues provided by the other's body, all pointing in the same direction. For example, neurons that were activated by eyes looking downwards also responded when head or body orientation was directed downwards. However, if eyes, head and body cues were incongruent, the eye gaze dominated, overriding the information on head direction. And in turn, information on the head direction seemed to override information provided by body orientation.

Bruce et al. (1981) were the first to describe a population of neurons in STS that was selectively responsive to faces in single cell recordings in macaque monkeys, emphasizing the extraordinary role of face perception in primates. A later study reported that 64% of cells responsive to faces and profile were also dependent on the position of the eyes (Perrett et al., 1985). Interestingly, Yamane et al. (1988) could show that a population of cells preferably responsive to eye gaze, did not need additional face features to be activated, but was only relying on eye gaze. These studies suggest that the monkey STS contains a neural system exclusively processing gaze direction (Langton et al., 2000).

Several studies have tried to delineate the exact topography of gaze following related signals in the STS of monkeys: Kamphuis et al. (2009) trained monkeys to exhibit gaze following in an fMRI scanner, an approach that allowed the

authors to identify a region in the posterior part of the STS that was selectively activated when monkeys performed head gaze following. Marciniak et al. (2014) performed a similar experiment and could show that the area in pSTS responsible for mediating gaze following in monkeys is not overlapping, but still close to one member of the face patch system, previously described by Tsao et al. (2003): the medial face patch.

In humans, several fMRI studies reported BOLD (blood oxygen level dependent) activity in anterior regions of the STS evoked by the perception of faces in which the mouth or the eyes were moving (Puce et al., 1998) and activity in posterior parts of the STS region by the perception of body movements for instance in dancing (Howard et al., 1996). A PET (positron emission tomography) experiment on humans detected activity in portions of the left STS, elicited by meaningful movements, but not by gestures lacking meaning (Rizzalotti et al., 1996). These studies strongly suggest that cell populations in the STS are not activated by body motion per se, but are sensitive to movement providing social information and also to static social cues, therefore playing an important part in social perception (Allison et al., 2000).

Bentin et al. (1997) recorded ERPs (event-related potentials) on the lateral temporal scalp in humans and reported on larger responses when eyes were presented isolated compared to the presentation of full faces, reflecting the extraordinary value of eyes and eye gaze encoded on a neuronal level. Early fMRI (functional magnetic resonance imaging) studies in humans showed activation in parts of the posterior part of the STS region, close to V5, when visual stimuli showed an alternation of averted and facing gaze (Puce et al., 1998). Moreover, Pelphrey et al. (2003) were able show that discrete regions of the STS are not only activated when a subject views a face in which the eyes shift their gaze, but that the STS is extremely sensitive to the social context in which gaze shifts occur.

Hoffman and Haxby (2000) performed an fMRI study on humans that showed that a distinct area in the posterior part of the STS was exclusively activated by the perception of eye gaze. An additional study on gaze processing was able to show that the pSTS is not only responsible for the perception but also for extracting the directional information from eye gaze (Hooker et al., 2003). Materna et al. (2008) reported on activity in pSTS in an fMRI experiment in humans, while subjects performed gaze following, arguably responsible for the geometric calculations needed to shift one's own gaze in accordance to the gaze orientation of the other, they called this are the 'gaze following patch' (GFP). In a follow-up study Marquardt et al. (2017) could show that in humans this GFP is distinct from any of the neighboring face patches, not overlapping but still located in the same region of the posterior STS.

1.1.3. Neural Correlates of Social Cognition

As elaborated before, gaze following, joint attention and Theory of Mind are major underpinnings of viable social interactions. The STS region is a major player in this context, but nevertheless has to be considered as part of a larger network of brain areas and brain functions as it interacts with other parts of the brain. On one hand the STS region receives information from the visual cortex (Oram and Perrett, 1996), on the other hand it is forwarding information to the amygdala and orbitofrontal cortex (OFC) (Wicker et al., 2003) that are key players in controlling social cognition. For instance, in PET studies on human social interaction engaged in gaze monitoring, activity is found in the STS as well as the amygdala and orbitofrontal cortex (Kawashima et al., 1999, Wicker et al., 2003). Considering these and other findings, Emery (2000) suggested that the STS region is essential for recognizing eyes, faces and bodies as stimuli, whereas the amygdala and orbitofrontal cortex are adding emotional value and social relevance. Allison et al. (2000) on the other hand claimed that the initial analysis of social cues, with regard to social relevance and deeper meaning, also occurs in the STS region, based on results on context dependent

activation of cells in STS such as goal directed and meaningful gestures (see above).

STS, the amygdala and OFC are considered to only play the major parts (Baron-Cohen, 1995; Wicker et al., 2003) in this context, but besides these three areas there are additional brain areas, such as precuneus, posterior cingulate cortex and more, contributing to the progress. Ochsner et al. (2004) reported on activity in the (left) precuneus as well as in the posterior cingulate when emotions needed to be attributed to oneself as well as to other people. Furthermore, the precuneus is especially involved in taking in a third person perspective (Vogeley et al., 2004), which is essentially needed to understand other people's actions and intentions. To take in a third-person perspective, one has to be aware of what a counterpart would think, feel and intend to do. This kind of awareness is an important part of the 'mindreading system' (Cavanna and Trimble, 2006). Attributing thoughts and intentions to other people and simultaneously distinguishing one's own thoughts and intentions is essentially needed to create a Theory of the other's Mind.

1.2. Cognitive Control

1.2.1. Automatic, Learned and Controlled Behavior

According to Miller et al. (2002) human behavior can be separated into 3 groups: automatic behavior, learned behavior and controlled behavior. In everyday life most of our behavior is automatic. For instance, we do not need to voluntarily decide to blink when something is thrown towards our face. Reflexive and automatic movements are based on preformed and little flexible circuits shaped by millions of years of brain evolution. They allow fast reactions, even without paying attention.

Some useful motion sequences are fixed in mind, because they have been repeated so often that they become familiar. Learned behavior is helping us for instance when driving a car. One does not pay attention to traffic lights and signs consciously, but is finding one's way based on visual cues processed in a bottom-up manner. In the context of driving or locomotion, external stimuli arising from the environment determine behavior like accelerating or braking. Miller et al. (2002) called this 'well established neural pathways waiting to be fired off by the correct input'.

If something unexpected happens one is forced to take control and to be in charge of what to do next. If someone is walking on the street in front of the car, there is no habituated behavior, no established neural pathway to rely on. One has to rely on additional abilities of the brain: controlled behavior. By relying on experience, knowledge and internal goals one can judge the options and decide on what to do next. In this scenario internal information/motivation trigger consecutive behaviors in a top-down hierarchy (Miller et al., 2002).

Cognitive control involves different aspects such as implementing a rule, context dependent decision making, response inhibition and performance adjustment (see below). All these aspects share that they are led by internal goals in a top- down manner. Lately cognitive control of behavior has been an intensely studied topic and researchers have been especially interested in its specific location within the human prefrontal cortex.

1.2.2. The Prefrontal Cortex

The prefrontal cortex (PFC) is a phylogenetically relatively recent part of the cerebral cortex. It has its largest size in humans and might be what distinguishes humans from animals in terms of cognitive abilities (Fuster, 1995). The prefrontal cortex is interconnected to brain areas processing external information (sensory cortex areas), motor structures and internal information (limbic system, midbrain) (Miller and Cohen, 2001). The PFC not only collects information from these structures but in turn provides feedback, i.e. in most cases connections are reciprocal. This wide range of interactions within the brain enables the PFC to be well suited for summarizing information and exerting control over behavior (Nauta, 1971).

In an experiment by Miller et al. (2002) monkeys were presented pictures of cats and dogs as well as exemplars offering morphed variants involving features of the respective other species category. The observers were asked to decide which of the two categories the shown exemplar belonged to. As long as the features of one species dominated, the monkeys were able to choose the dominating species category very precisely (90% correct answers) even though elementary features, such as the outline of the body, might have pointed to the other category. This result suggests that the monkeys classified the pictures based on a quasi-holistic percept rather than based on low level features. In this experiment single cell recordings from lateral PFC detected neurons, which seemed to encode category membership, distinguishing cat-like dogs and dog-like cats as precisely as the monkeys performed in the experiment. These results suggest that the PFC encodes category information rather than low level sensory features.

To test for rule learning conditional learning tasks are typically used. Here the task is not only based on the stimulus itself, but additionally on contextual information. Wallis et al. (2001) trained monkeys to react in different ways depending on whether two consecutive pictures were the same or different. The monkeys had been trained to rely on a match to sample rule: for instance, in case the stimulus matched the preceding one, they had to press a button and

withhold pressing otherwise. Alternatively, they were instructed to press the button in case of the non-matched and to not respond to a matched pair. Whether to respond to a matched or a non-matched pair dependent on an additional rule cue. Monkeys performed very well and their ability to decide between matched and non-matched pairs was above chance level even when confronted with sample stimuli not seen before. This suggests that rather than learning associations for each and every stimulus monkeys had implemented the rule they would stick to. The study also showed that rule selective neurons had a higher activity when the 'respond to a match'-rule was at stake rather than the other one, a difference that was independent of the physical properties of the rule cue. In sum these findings clearly indicated that the neurons in PFC do not reflect physical properties but the abstract rule itself. A similar conclusion could be drawn from a study by Asaad et al. (1998) who trained monkeys to react to a given object with a saccade to the left or the right, depending on the prevailing rule. Interestingly, in many neurons the authors observed a shift in baseline activity when the monkeys were told to switch between rules. In summary, categories and behavior guiding rules are implemented in the PFC and used for planning voluntary behavior (Miller et al. 2002).

The PFC also accommodates the neuronal underpinnings of inhibitory, or more general, executive control, allowing the PFC to gate functions accommodated by other brain structures. Inhibitory control is understood as 'Suppression of inappropriate responses, stimulus-response mappings or task set when the context changes' (Aron et al., 2004). Another definition would be 'the mechanism or set of processes that result in the containment of prepotent behavioral responses when such actions are reflexive-like, premature, inappropriate or incorrect' (Burle et al., 2004). Lesion studies in monkeys and more recent fMRI studies in humans could locate inhibitory control in the dorsolateral prefrontal cortex (dlPFC) and ventrolateral prefrontal cortex (vlPFC). Non-human primates could learn to suppress behavior if confronted with 'no-go stimuli', however, following lesions of the vlPFC this ability was compromised (Iversen and Mishkin, 1970). Neuroimaging studies in humans,

using a go vs. no-go paradigm detected task-related activity not only in the dlPFC (de Zubicaray et al., 2000) but also the vlPFC (Bunge et al., 2002).

The studies presented before seem to suggest a high degree of topographical specialization of functions within distinct parts of the PFC representing distinct functions. Yet, this is a view that has been challenged by others arguing that already the assumption that different cognitive modules might be separable is questionable (Ridderinkhof et al., 2004). Notwithstanding this controversy, there can be little doubt that the PFC is a part of the brain that is essential for the modulation of processing in other cortical as well as subcortical areas and structures respectively, required in order to meet demands of current as well as long-term goals (Miller and Cohen, 2001).

Successful cognitive control of behavior requires information of the efficiency of the attempt to suppress unwanted behavior and information on the efficacy of the preferred behavior. Hence, actions need to be monitored. Based on fMRI experiments and computational modeling Botvinick et al. (2001) concluded that the control processes and adaptive regulations discussed before are located in the lateral PFC, whereas performance monitoring is located in the anterior cingulate cortex (ACC). MacDonald et al. (2000) used a version of the Stroop task to dissociate the different functional roles of dlPFC and ACC in cognitive control and performance monitoring. In the Stroop task subjects are asked to either name the color, in which a colored word is displayed, for example the word '*red'* displayed in green - a color naming task - or to just read out the word displayed – a word reading trial. In their experiment they added a delay between presentation of the instruction and the presentation of the stimulus. The authors detected early activity in the dlPFC representing the implementation of the rule and later activity in the ACC interpreted as reflection of performance monitoring, a control signal needed to survey behavior in accordance to the rule represented by the dlPFC. Kerns et al. (2004) detected that larger activity in the ACC during error trials was followed by larger activity in the lateral PFC and greater post-error adjustment in behavior, suggesting a tight link between the ACC and lateral PFC. The monitoring signal might reflect

behavioral failures or, alternatively the experience of conflicts or decision uncertainty, an information then thought to be used by control processes in the lateral PFC to adjust behavior (Ridderinkhof et al., 2004). In sum, all authors agree on complementary roles of the dlPFC and ACC in cognitive control: the dlPFC implementing the rule and the ACC monitoring performance and, if needed, indicating to strengthen control.

Patients suffering from damages to the PFC seem to be quite inconspicuous at first glance. However, on closer examination they exhibit difficulties in sustaining attention and keeping 'on task'. Their behavior may become very impulsive, for example randomly grabbing items being set in front of them. Baddeley and Della Sara (1996) called this the 'dysexecutive syndrome'. Patients with lesions in PFC are able to follow simple instructions, but are unable to follow or even set up a series of routines, because they keep being distracted by any upcoming stimulus and forget about what to do next (Shallice and Burgess, 1991). One might call this 'goal neglect' (Duncan et al., 1996). Deficits in sustaining attention can not only be seen in patients with PFC damage but also in children with ADS/ADHS. Anatomical studies on such children have described abnormalities in prefrontal brain areas, especially in the vlPFC (Casey et al., 1997). Abnormalities of the vlPFC may also lead to disturbances of inhibitory control. At any rate patients with large damage of the vlPFC take much longer to react to stop-signals (Aron et al., 2003). When performing the Stroop task PFC patients did not have difficulties in following the instructed rule in the first place but to cope with sudden changes of the rule, suggesting an impairment of working memory (Milner, 1963). An additional aspect of clinical studies was that in general patients did not show any difficulties in object recognition. It has often been argued that in many of the monkey experiments discussed before, the animals might have been relying on the physical shapes of the objects. The fact that patients did not show any impairment of this ability is a strong argument in support of the notion that the PFC is dealing with abstract rules and categories rather than being responsible for identifying objects on their physical basis (Miller and Cohen, 2001).

1.3. Underpinnings of the BOLD (blood oxygen level dependent) Signal in Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is an excellent technique to non-invasively measure neuronal activity in humans. It combines both a high spacial resolution as well as a good coverage of the whole brain.

The fMRI technique is essentially based on the coupling of cerebral blood flow (CBF), energy demand, and neural activity. These interactions are not only complex but also rely on additional features like the type of neural activity involved, the cell population generating this activity and the relation between this neural activity and energy demands (Logothetis, 2003).

The BOLD signal was first described by Ogawa and Lee 1990, in a study on rat brains in a 7-Tesla-scanner. They discovered black lines of varying thickness when using a very high resolution for brain images (65 x 65 x 700µm^3) that were only visible in images acquired with a gradient-echo pulse sequence but not in regular spin echo sequences. The black lines turned out to be signals of blood vessels. The group discovered that the MR signal decreased when the oxygen level of the air was reduced and vice versa the MR signal was increased when the oxygen level of the air was elevated again. Furthermore, the authors could show that this effect was not limited to the blood vessels but also applied to the surrounding tissue (Ogawa et al., 1990). Further support for this hypothesis came from a study on cat brains during anoxia, showing lower MR signal with decreasing oxygenation of the blood (Turner et al., 1991). Ogawa et al. (1990) concluded that this BOLD contrast adds an additional feature to magnetic resonance imaging and complements other techniques that are attempting to provide positron emission tomography-like measurements related to regional neural activity. This discovery marked a breakthrough in non-invasive brain imaging. First studies in humans used paramagnetic contrast agents (gadolinium) to detect changes in cerebral blood volume (CBV) using high-speed echo planar imaging techniques (Belliveau et al., 1991; Rosen et al., 1991). But soon, first groups obtained results in humans without using any

contrast agents but relying only on the described BOLD signal (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1992).

The BOLD effect is based on two characteristics: a biophysical and a physiological one: Oxyhemoglobin is known to be diamagnetic (i.e. essentially nonmagnetic) whereas deoxyhemoglobin is parametric, meaning deoxyhemoglobin having shorter T2* and hence a lower MR signal. Second, the increased consumption of oxygen by neuronal activation is accompanied by a dysproportional/overshooting supply of fully oxygenated blood. Consecutively downstream the activation area the concentration of deoxyhemoglobin is decreased, T2* elevated and the MR signal increased. (McRobbie et al., 2006; Buxton, 2002). By using a gradient-echo pulse sequence and its strong T2* weighting, the susceptibility of deoxyhemoglobin was increased and thereby Ogawa discovered a technique to measure these changes in the blood oxygen level.

Today we are aware of the fact that the BOLD signal is not only dependent on the blood oxygen level but also on additional variables such as cerebral blood flow and cerebral blood volume (Boxermann et al., 1995; Buxton and Frank, 1997; Ogawa et al., 1998). Despite this complexity and multiple variables intervening, a deeper understanding of how the BOLD signal is related to the underpinning mechanisms is crucial to understand the relation between the measured signal and the underlying neuronal activity we think it is representing (Logothetis, 2003).

To study this relationship, it is necessary to take a closer look at the hemodynamic response over space and time. Therefore numerous studies have focused on the time course of the BOLD signal (Figure 4). The onset of the hemodynamic response is delayed by approximately 2 seconds after the onset of the stimulus (Kwong et al., 1992), which is approximately the time it takes blood to travel from arteries through capillaries to the veins. The signal would reach its plateau after 6-12 seconds and return to baseline after another 6-12 seconds. (Frahm et al., 1996; Logothetis et al., 1999). Frequently, instead of

returning to baseline a poststimulus undershoot can be recognized and is probably due to vasodilatory mechanisms caused by the increased blood flow (Buxton et al., 1998).

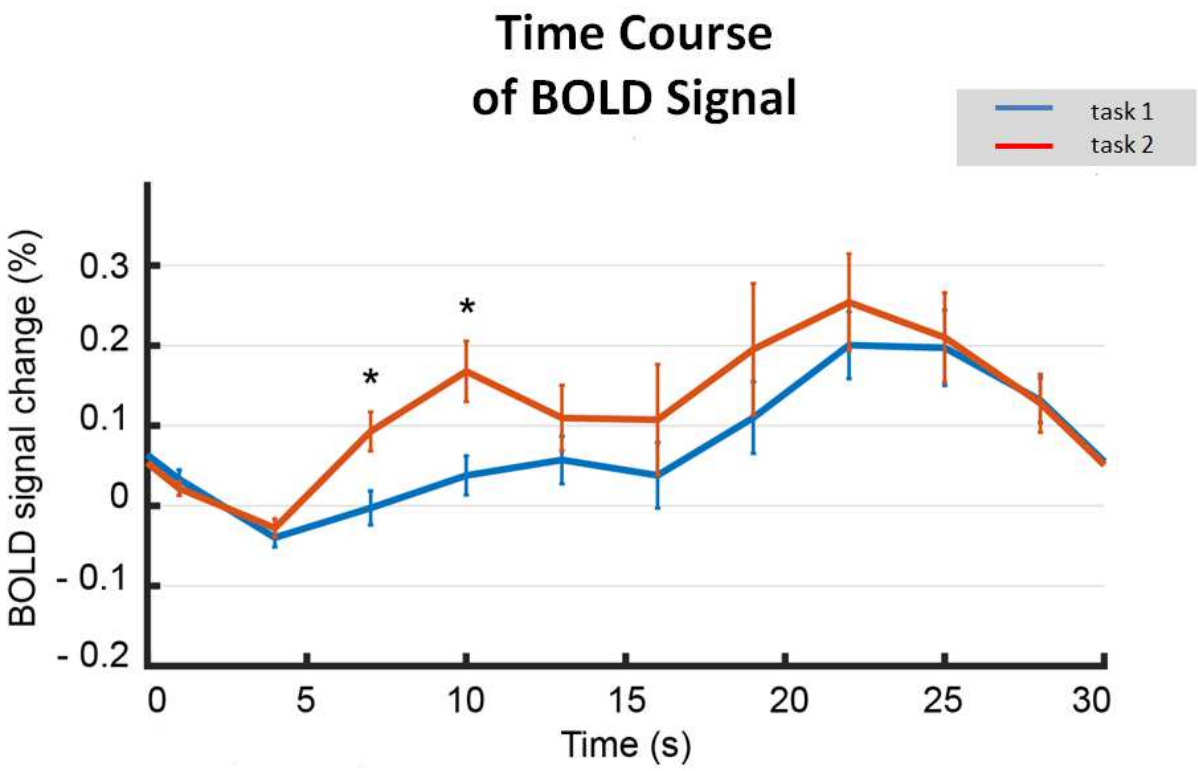

Figure 4: Example of time course analysis of BOLD (blood oxygen level dependent) signals for two different tasks in a brain region (n = 20). The BOLD signal rises approximately 4 seconds after onset of the trial and would return to baseline after approximately 30 seconds. The asterisks (*) are indicating significant differences between task 1 and task 2.

Several studies propose a linear relationship between neural activity and BOLD response (Brinker et al., 1999; Ogawa et al., 2000). Rees et al., (2000) compared results from human fMRI with electrophysiological data from single cell recordings in monkeys. They used a visual perception paradigm and compared measurements from the human middle temporal visual area (MT), which is considered to be homologues presented in monkeys' MT, with monkey

data from MT or V5. The authors suggested that the BOLD signal is directly proportional to the average firing rate of the neurons. An additional study by Logothetis et al. (2001) would combine both measurements and simultaneously acquire electrophysiological data and fMRI response in monkeys. The authors found a direct relation between the BOLD signal and an increase in local neural activity. The BOLD signal was linearly correlated to the local field potential (LFP), the multiunit activity (MUA), and the firing rate of small cell populations.

Taken together, the results from fMRI and electrophysiological recordings suggest that the BOLD response directly reflects the neuronal activity caused by a stimulus. In a first approximation it seems like BOLD responses and neural responses are linked in a linear manner for paradigms with a short stimulus representation (Logothetis, 2003).

1.4. Current Study

Nonverbal communication is essential for successful social interaction. The face and especially the eyes carry important information on one's mental state (Andrew, 1963; Kobayashi et al., 1997; Emery, 2000). The direction of gaze can inform us about an object someone is interested in and, by following that gaze and focusing on the same object, humans establish joint attention. This ability allows the observer to attribute intentions and desires to the counterpart and to create a Theory of the other's mind (Perrett and Emery, 1994; Baron-Cohen, 1994, 1995b; Langton et al., 2000).

Gaze following is embedded in a broad behavioral context, depending on a large range of external influences, such as the identity of a counterpart (Liuzza et al., 2011) and his/her social status (Dalmaso et al., 2012), familiarity (Deaner et al., 2007) and also face age (Ciardo et al., 2014). Gaze following is considered to be a fast and reflexive-like behavior (Hood et al., 1998; Friesen et al., 1999; Driver et al., 1999; Langton et al., 2000; Batki et al., 2000), yet it can be suppressed whenever it seems to be inappropriate in a situation. This could

be not to behave in an impolite manner or to cover one's own interests. Previous studies were able to show that the neural substrate of gaze following is a well-defined region within the posterior Superior Temporal Sulcus (pSTS) (Materna et al., 2008; Marquardt et al., 2017), referred to as the 'gaze following patch' (GFP). This area is responsible for the underlying geometrical calculations necessary to shift one's gaze in accordance of the gaze direction of the counterpart (Materna et al., 2008; Marquardt et al., 2017; Kraemer et al., 2020; Ramzanpour et al., 2020).

Based on this knowledge we were interested in locating brain regions modulating gaze following in accordance to the special needs of a situation or one's internal interests. We assumed this region to be located in prefrontal areas, since execution of cognitive control and modulation of subsequent brain areas has to be considered a higher cognitive function, which is located in phylogenetically younger parts of the brain. To detect neural substrates of cognitive control of gaze following, we designed an fMRI experiment, in which our subjects were exposed to gaze following cues and had to, depending on the instruction, perform gaze following and establish joint attention or ignore the gaze cue. We expected this design to help us locate a higher ranking area in the prefrontal brain regions that executes a control function on pSTS in a top-down manner.

2. Methods

2.1. Subjects

20 subjects (10 female, 10 male) participated in our study. Subjects were between 20-32 years old, right-handed and had normal or corrected-to-normal (lenses) vision. The study was approved by the Ethics Review Board of the Tübingen Medical School (664/2014BO2) and complied with the guidelines of the Declaration of Helsinki. All subjects received oral and written information and provided written consent to participate in our study. Furthermore they received an expense allowance.

2.2. Experiment

The images presented were provided by Marquardt and colleagues (2017). They were portraits of a white, Caucasian female (‘sender’) and manipulated using Adobe Photoshop 7.0. Fixation picture showed the ‘sender’ in front of a random pattern background (gray and black dots). Her eyes were straight ahead and the color of her iris was green. In front of her were 5 targets, all the same in size and shape, but each with a different color (from left to right: dark blue, light blue, green, light brown, dark brown). The visual angle between the targets was 12.5° for the ‘sender’ (Figure 5).

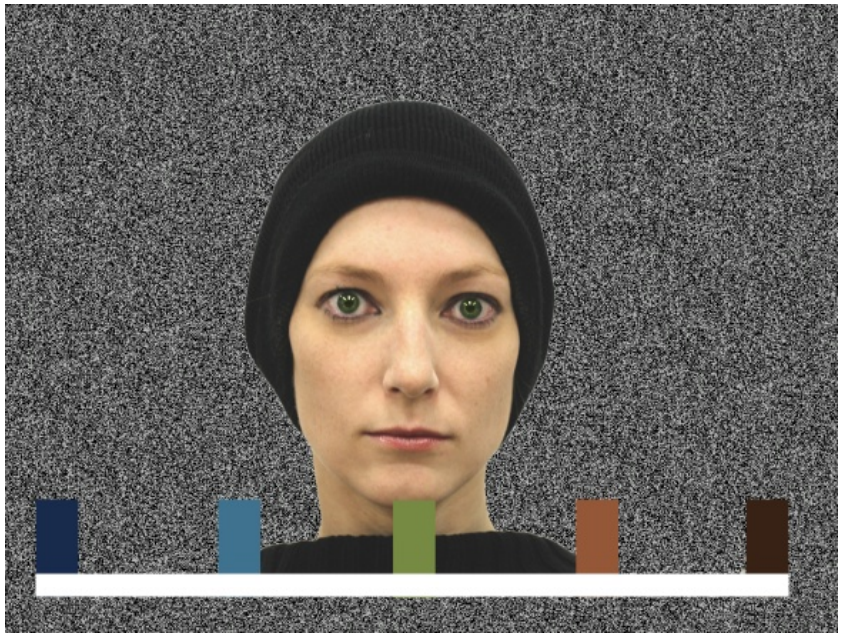

Figure 5: Fixation Picture. Green eyed 'sender' looking straight ahead. In front of her are 5 targets in different colors.

For the following spatial cue epoch task pictures were manipulated in two aspects: the position of the eyes changed, so the 'sender' would no longer looked straight ahead, but was instead looking at one of the 5 targets; and also the color of the eyes changed (dark blue, light blue, green, light brown, dark brown), corresponding to the color of one of the 5 targets. Since there are 5 different targets the 'sender' would look at and 5 different colors the iris could change to, the whole set consisted of 25 task pictures and one fixation picture.

In our experiment subjects were instructed to perform two different tasks: 'gaze following' and 'color mapping' (Figure 6). In a 'gaze following trial' subjects were asked to perform a saccade to the target the 'sender' was looking at, ignoring the changing color of the iris. For a 'color mapping trial' subjects were asked to perform a saccade to the target corresponding to the color of the iris in the task picture, this time ignoring the direction of the eyes.

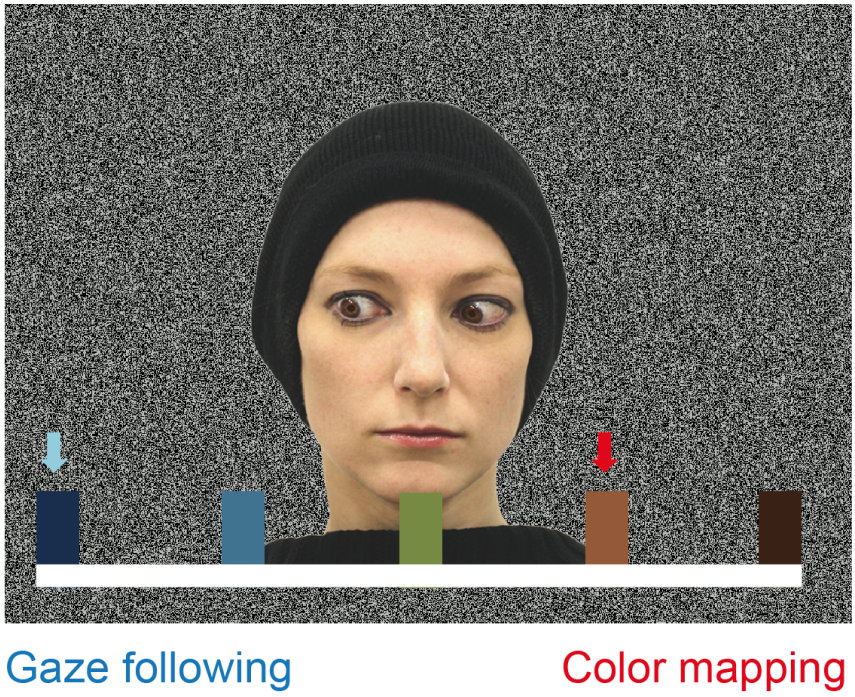

Figure 6: Task Picture. Direction of gaze and color of iris changed.
The arrows are pointing to the correct target for the task labeled below.

'Gaze following' and 'color mapping trials' could either be presented in blocks, when the instruction was announced only once for all of the following trials, or event-related, when an instruction was given before each and every trial (Braver et al., 2003). We decided on this mixed design using blocks and event-related trials in the same experiment to distinguish between sustained and transient cognitive control in gaze following. This design would not only allow us to distinguish between different areas involved in cognitive control processes, but on the other hand would also give us more information about the automaticity of gaze following and the mechanisms it is subordinated.

When trials were presented in block design, subjects once received the written instruction whether to perform 'gaze following' or 'color mapping' for all consecutive trials within this block (Figure 7). After a delay of 5 seconds, during which subjects were asked to keep their eyes straight on the red fixation point (dimension: 0.3°), the fixation picture was presented for 5 seconds, subjects still focusing on the red fixation point. The spatial cue was displayed for 4 seconds

and the red fixation point would be removed 1 second after its appearance. This was used as go-signal for subjects to perform a saccade to one of the five targets. Subjects were asked to keep focusing on the target until the red fixation point would reappear and the next trial started. Subjects performed 5 trials in one block.

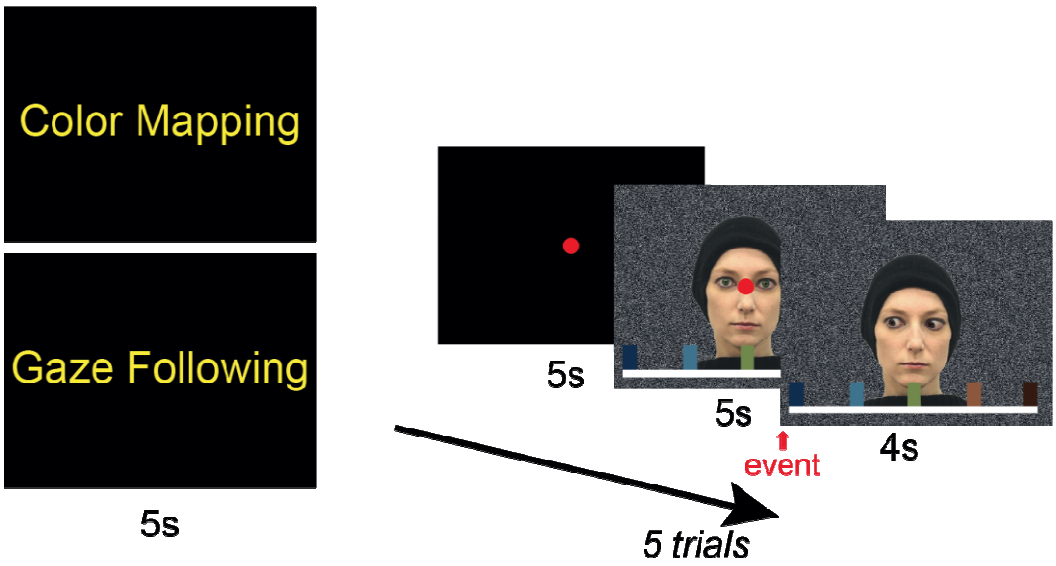

Figure 7: Time Line of Block Design
Subjects either performed a 'gaze following block' or a 'color mapping block'. After announcement of the task there was a delay of 5 seconds, followed by the fixation picture. When the task picture was shown the fixation point disappeared after 1 second and the subject performed a saccade to one of the targets. With a delay of 5 seconds the next trial would start.

For the event-related design subjects once received a written instruction on the monitor: 'Gaze Following/Color Mapping' so they were aware that for the consecutive trials the task would be announced before each trial to shift the tasks randomly. We decided to pseudo randomize trials, allowing no more than 3 consecutive trials dealing with the same task. The intertrialdelay, a red fixation point (dimension: 0.3°) on a black screen, was randomized between 14-15 seconds to diminish overlapping effects of the BOLD response by the previous trial (Dale, 1999; Bandettini and Cox, 2000). Again subjects were asked to keep their eyes straight on the red fixation point whenever visible. After presenting

the instruction for the upcoming task, we added another delay of 1-5 seconds before the fixation picture (5 seconds) and task picture (4 seconds) appeared to adapt the structure from the trials we used in block design. The red fixation was constantly visible and disappeared 1 second after the presentation of task picture. This was used as go-signal for subjects to perform a saccade. There were 15 consecutive trials presented in event-related design.

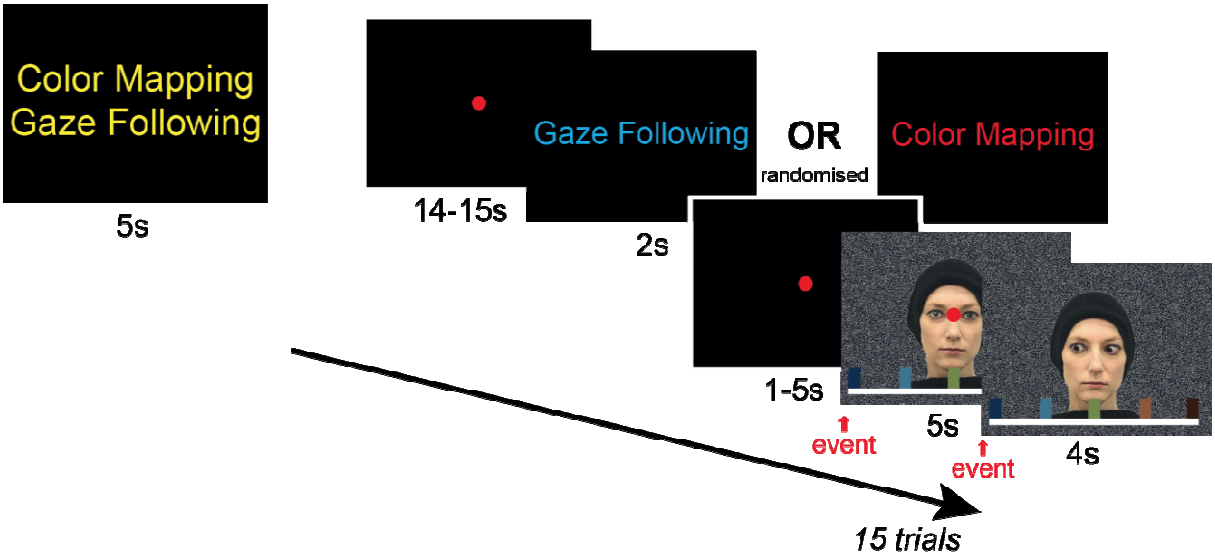

Figure 8: Time Line of Event-Related Design
The yellow instruction indicating the upcoming event-related design was only presented once. After a delay of 14-15 seconds subjects received a second instruction only for the consecutive trial. Another delay of 1-5 seconds was added before the fixation picture appeared. When the task picture was presented the fixation point disappeared within 1 second and subjects performed a saccade. The consecutive trial would start with after a delay of 14-15 seconds.

The whole experiment consisted of a 'gaze following block' with 5 trials that was followed by an event-related part with 15 trials. After this there was a 'color mapping block', also consisting of 5 trials, and finally another event-related part with 15 trials. One experiment lasted approximately 17 minutes and each subject performed three experiments.

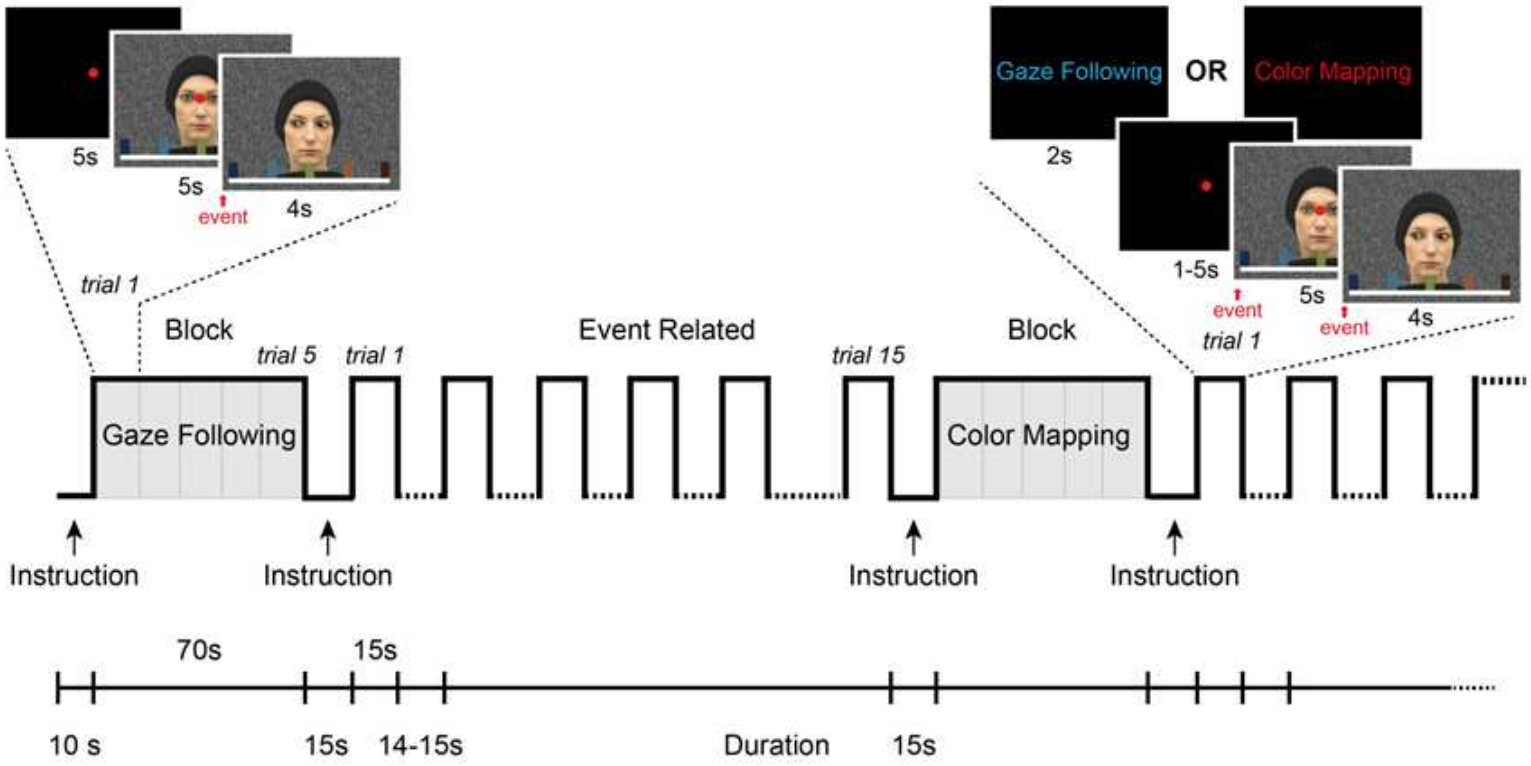

Figure 9: Time Line of the Complete Experiment.
The red arrows indicate the events that were set for analysis of the data at the onset of the fixation picture and the onset of the task picture

2.3. Recording

All subjects completed a training session to make them familiar with the tasks and the experimental design before performing the experiment in the MRI scanner. Furthermore we used this session to improve subjects' performance by giving feedback on blinking and fixation. Training lasted approximately 45 minutes and took place in a darkened room. Participants were sitting on a chair in front of a screen (distance: 90cm, dimension: 120cm x 80cm, size of images presented: 40cm x 30cm projected from the back by a beamer) and were asked to rest their head in a chin rest to prevent head movement.

Scanning took place 1-5 days later. Subjects lay supine in the MRI scanner and their heads were fixed by foam rubber to minimize head movement. Visual stimuli (dimension: 45cm x 34cm) were projected on a translucent screen positioned behind the subject and seen via a mirror attached to the head coil so subjects could easily perform the task in their horizontal position. The resulting distance between subjects and image was 102cm. Images were acquired by a 3-Tesla MRI scanner (Prisma, Siemens, Erlangen, Germany) using a 12 channel head coil (acquisition matrix: 64x64). A volume of approximately 1200 T2-weighted echo-planar (epifid) images (TR: 3000ms, TE: 35ms, TA: 2.93s, flip angle: 90°) was taken. These pictures covered the whole brain (44 transverse slices, slice order: [44:-1:1], slice thickness: 2.5mm, gap: 0.5mm, pixel spacing: 3mm x 3mm). Additionally an anatomical T1-weighted image was taken for each subject, therefore using a magnetization prepared, rapid acquisition gradient-echo sequence (mprage) (TE: 2.96ms, TR: 2300ms, TI: 1100ms, flip angle: 8°, voxel size: 1.0mm x 1.0mm x 1.0 mm).

Vertical and horizontal eye movements were recorded in both training and scanning sessions. Eye position recordings during training were acquired using a Cronos Vision C-ET video eye tracker. These data were not analyzed but mainly used to evaluate subjects' performance and to improve it by feedback on blinking and fixation, to provide useable data during scanning. During scanning we used a certificated, MRI-compatible eye-tracker (SMI iView X™ MRI-LR;

sapling rate: 60Hz). Calibration on a nine-point-grid was conducted before each of the three runs, to improve the quality of data.

2.4. Data Analysis

The whole volume of images of each subject was preprocessed and analyzed using a program for statistic parametric mapping: SPM8 (Welcome department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm/).

For preprocessing functional images were first realigned and slice time corrected. Anatomical image, mean image and functional images were coregistered to enlarge mutual information. Anatomical image was segmented using templates provided by SPM (T1.nii 1) and used to normalize functional images. Finally functional images were spatially smoothed using a full-width half-maximum Gaussian filter (FWHM: 6mm) (Friston, 2011).

Data analysis was performed by modeling the events of the two tasks (‘gaze following’ and ‘color mapping’) with a canonical hemodynamic response function and applying the general linear model (GLM) (Friston, 2011, Kiebel and Holmes, 2011). As onset times we used the appearance of the task picture or the appearance of the fixation picture. Regressors representing estimated head movements (translation and rotation with six degrees of freedom) were added into the model as covariates of no interest to account for head movements artifacts during scanning. In order to eliminate slow, not task relevant fluctuations, we also added a high pass filter of 1/128 Hz. For each subject, contrasts were calculated for ‘gaze following’ versus ‘color mapping’ and ‘color mapping’ versus ‘gaze following’ at the onset of the task in trials from block design and event-related design. Additionally we also calculated contrast of ‘gaze following’ versus ‘color mapping’, and vice versa, at the onset of the fixation for trials of the event-related design (the events used for statistical analysis are indicated by a red arrow in Figures 7-9). Significant changes were assessed using t-statistics.

In order to establish the response pattern for the group of subjects, single-subject contrast images were analyzed at a second level using a random effects model, comparing the average activation for a given voxel with the variability of that activation over the examined population (Friston et al., 1999a). BOLD responses were considered significant and reported if the statistical significance exceeded $p<0.01$, false discovery rate (FDR) corrected, at the level of single voxels and, moreover, involved clusters of more than 20 neighboring voxels. To optimally visualize and quantizes the cortical representations, statistical t-maps were projected onto inflated reconstructions of cortical surface gray matter using SPM 12 (http://www.fil.ion.ucl.ac.uk/spm/).

For additional analysis regions of interest (ROIs) were defined as spheres (radius 12mm) and centered on the peak activity coordinates of the group analysis for each area. Linear correlation analysis was performed on the average beta-values extracted from ROIs for each subject individually.

3. Results

3.1. Behavioral Performance

Eye data were provided for 19 out of our 20 subjects. We assessed the percentage of correct target-directed saccades and the response latencies, where response latency was defined as latency after disappearance of the red fixation point and the start of the saccade. The saccade onset was determined as the time of peak saccade velocity. Although this approach might overestimate saccade onset times, it would significantly reduce variance. Furthermore, to exclude predictive saccades, not necessarily driven by the stimulus of the paradigm, we excluded reaction times less than 200ms after the go-signal in all subjects.

For data analysis we performed a two-way ANOVA (Analysis of Variance) ($p>0.05$) for the two conditions, but only for trials of the event-related part. There was no significant difference between ‘gaze following’ and ‘color mapping’, neither in percentage of correct saccadic choices (‘gaze following’: mean: 83.4%, SD: 13.3%; ‘color mapping’: mean: 82.2%, SD: 13.3%) nor for saccadic reaction times (‘gaze following’: mean: 573.7ms, SD: 154.3ms; ‘color mapping’: mean: 560.2ms, SD: 120.3ms), indicating that both task were experienced equally demanding to solve.

In one out of the 20 subjects, the eye position records were too noisy to allow a reliable judgment of target choices and reaction times. This subject’s data was excluded from any further analysis.

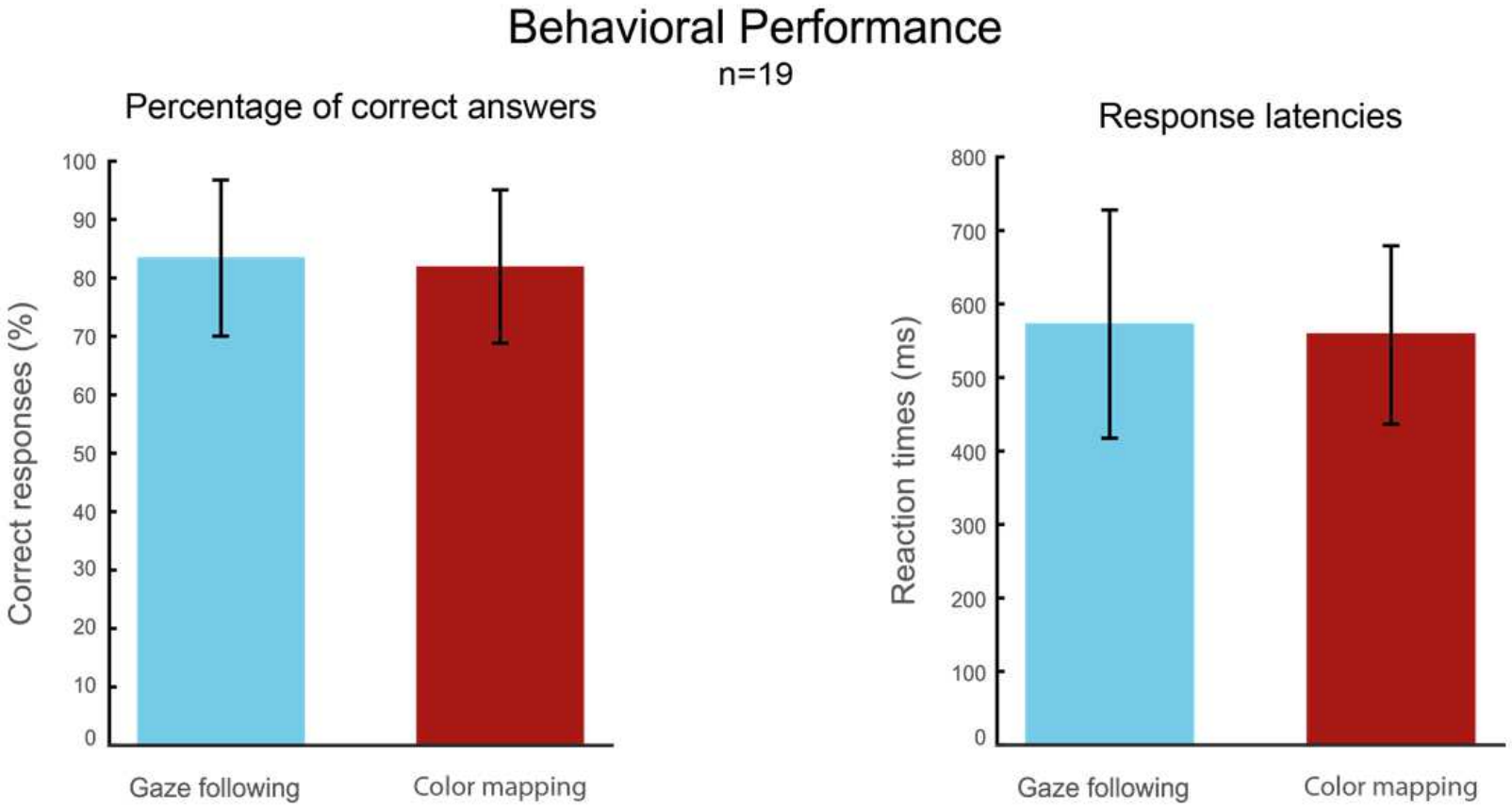

Figure 10: No significant difference (ANOVA, $p>0.05$) in behavioral performance for 'gaze following' and 'color mapping'. Data are only provided for trials from event-related design.

3.2. BOLD Response

We performed whole brain analysis comparing ‘gaze following trials’ to ‘color mapping trials’, subdividing them into groups: trials from block design and trials from event-related design. We included the block design to refer to as a control, but because of the low number of trials in ‘gaze following’ and ‘color mapping blocks’, the contrast only had very low significance and are not reported at this point.

For the following data analysis we only focused on trials from the event-related part, since we expected the effect we were interested in to be in need of a sufficient number of task switches. We should note that an event-related experimental design in general is statistically less powerful than classical block design experiments used before (Friston et al., 1999b). Hence, BOLD activity in the ‘gaze following patch’ did not pass the multiple comparisons correction ($p<0.01$, FDR-corrected), but only reached a statistical significance level of $p<0.05$ (uncorrected), cluster size: >5.

Besides this, we reasoned that the neural state representing the preparatory control mechanism must be established before the actual spatial cue becomes available in order to have enough time to act on the reflexive gaze following responses in ‘color mapping trials’. Hence, we were especially interested in the BOLD responses at a time window of 5 sec before the appearance of the spatial cue and aligned the events used for the analysis to the onset of the fixation picture (see Figure 8 and 9).

Comparing ‘color mapping trials’ versus ‘gaze following trials’ at the onset of the fixation picture, we found significant prefrontal activity in the left frontal cortex including dorsolateral prefrontal cortex (dlPFC) (peak MNI coordinate: **[x,y,z]=[-48, 26, 30]**), orbitofrontal cortex (OFC) **[x,y,z]=[-42, 47, -05]**, and the insula **[x,y,z]=[-36, 17, 10]**. We also found two clusters in the left and right posterior parietal cortex (PPC) **[x,y,z]=[-33, -55, 38]** and **[x,y,z]=[54, -52, 35]**, and bilateral precuneus **[x,y,z]=[-03, -64, 43]** and **[x,y,z]=[03, -64, 38]**, with significantly higher BOLD responses in ‘color mapping trials’ (Figure 10 / Table 1). Similar results could be achieved by comparing ‘color mapping’ versus ‘gaze following’ at the onset of the spatial cue period, revealing a prefrontal activation cluster in the left hemisphere in dlPFC (peak MNI coordinate: **[x,y,z]=[-48, 26, 30]**) and also in left parietal lobe (left PPC **[x,y,z]=[-33, -55, 38]** and right precuneus **[x,y,z]=[03, -64, 38]**) (Figure 11 / Table 2).

The reverse contrast, comparing ‘gaze following’ versus ‘color mapping trials’ at onset of the fixation, did not reveal any prefrontal activity. We detected BOLD response in an area located in the posterior temporal cortex (peak MNI coordinate: **[x,y,z]=[-51, -61, 03]**) congruent to the GFP with coordinates reported in previous studies from our lab very close (Materna et al.,2008; Marquardt et al., 2017). However, this GFP activity could only be observed with lowering the threshold to $p<0.05$, (uncorrected) but was also present during the subsequent spatial cue period after presentation of the task picture **[x,y,z]=[-51 -58 03]** ($p<0.05$ uncorrected) (Figure 12 and 13).

The preparation to follow gaze in gaze following trials, did not evoke a significant BOLD response relative to the baseline condition in any prefrontal or parietal regions when comparing ‘gaze following’ and ‘color mapping’ at onset of the fixation as well as during the spatial cue period, suggesting that the executive control signals are only required for suppression of the gaze following and not to initiate it.

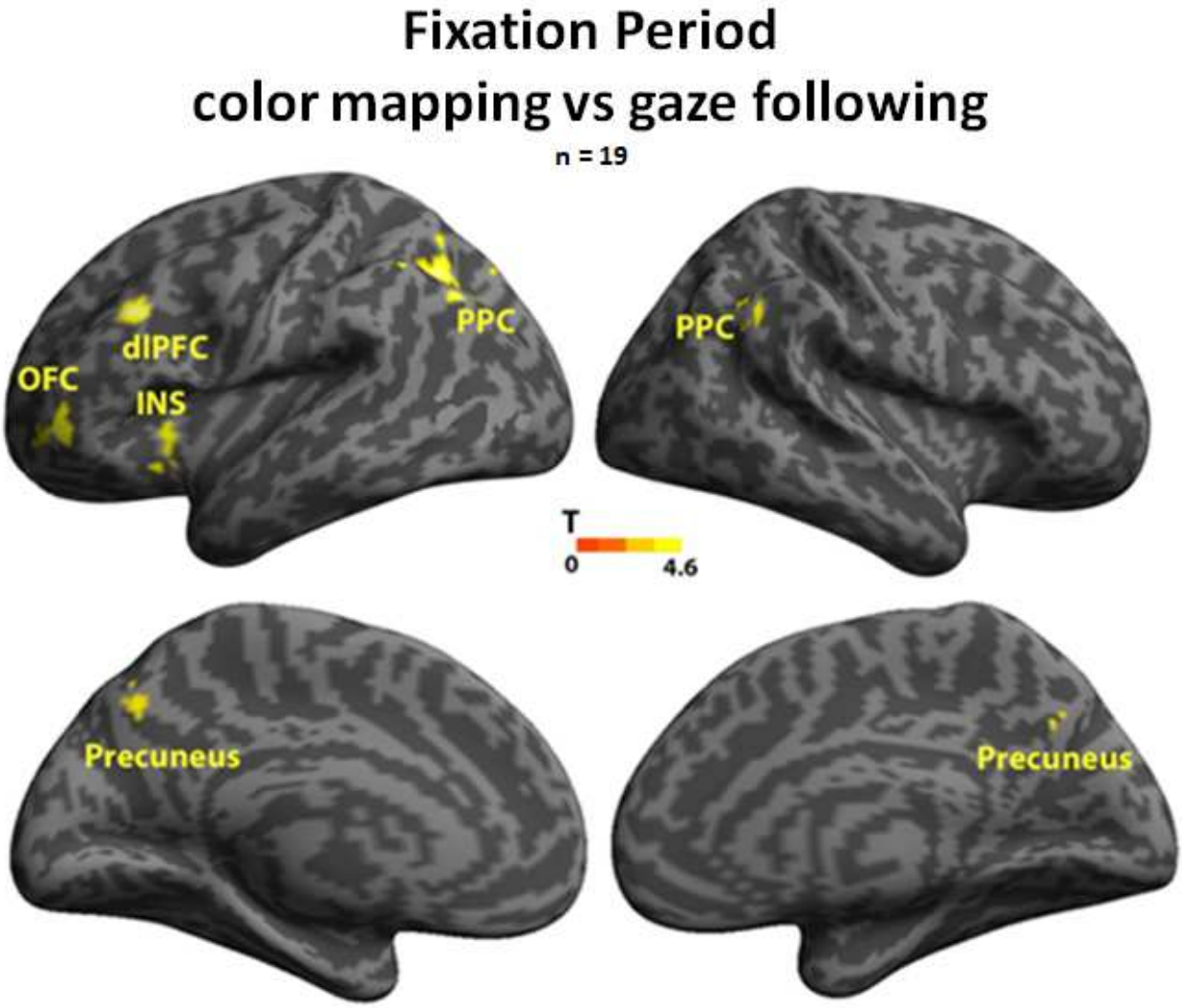

Figure 10: BOLD contrast during the fixation period between responses to the rule to suppress gaze and select a target based on eye color versus the rule to follow gaze. Significant clusters for 'color mapping' versus 'gaze following' were found in dorsolateral prefrontal cortex (dlPFC), orbitofrontal cortex (OFC), insula (INS), posterior parietal cortex (PPC) and precuneus ($p<0.01$, FDR-corrected, cluster size: 20).

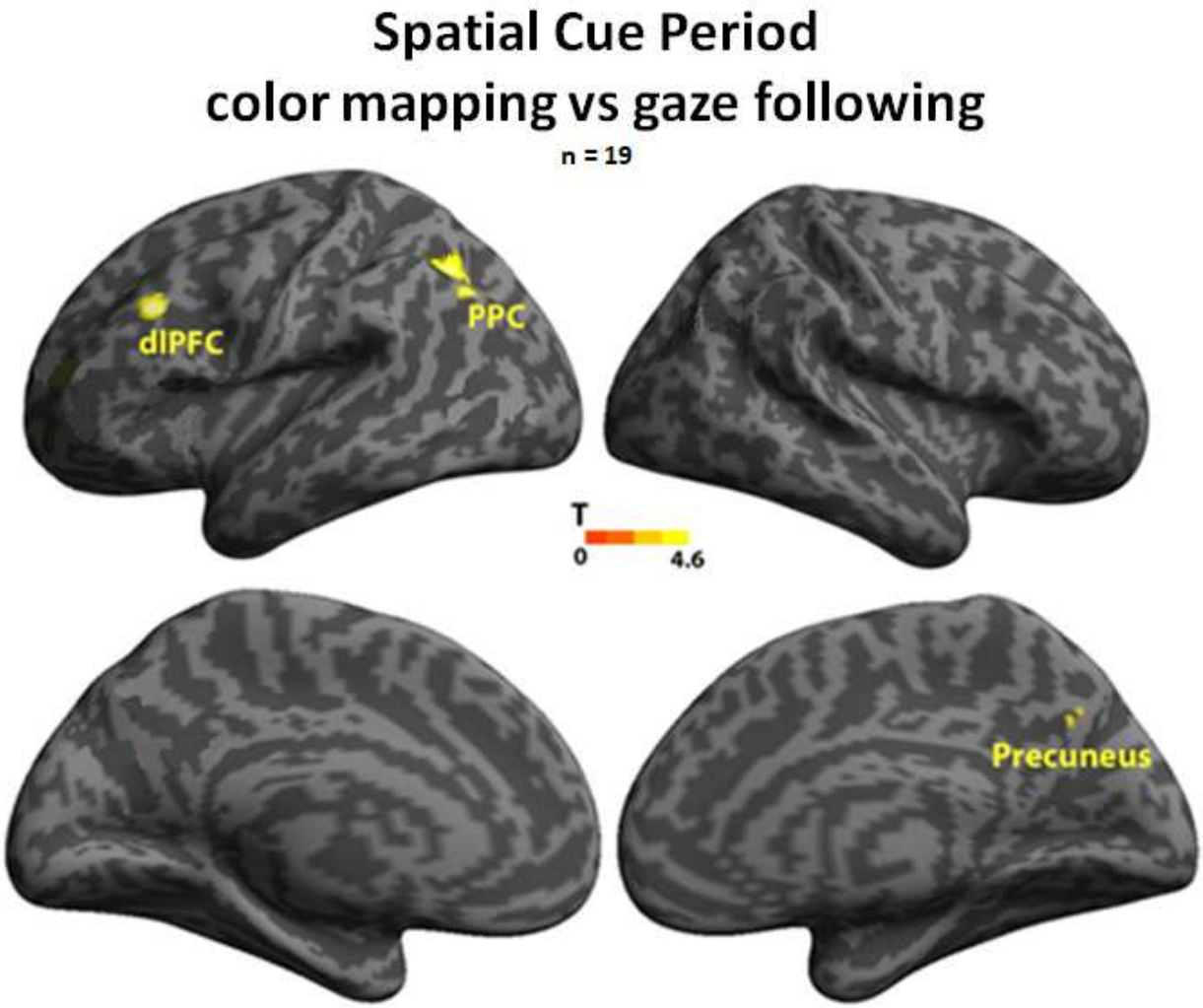

Figure 11: BOLD contrast during the spatial cue period between responses to the rule to suppress gaze and select a target based on eye color versus the rule to follow gaze. Significant clusters for 'color mapping' versus 'gaze following' were found in dorsolateral prefrontal cortex (dlPFC), posterior parietal cortex (PPC) and precuneus ($p<0.01$, FDR-corrected, cluster size: 20).

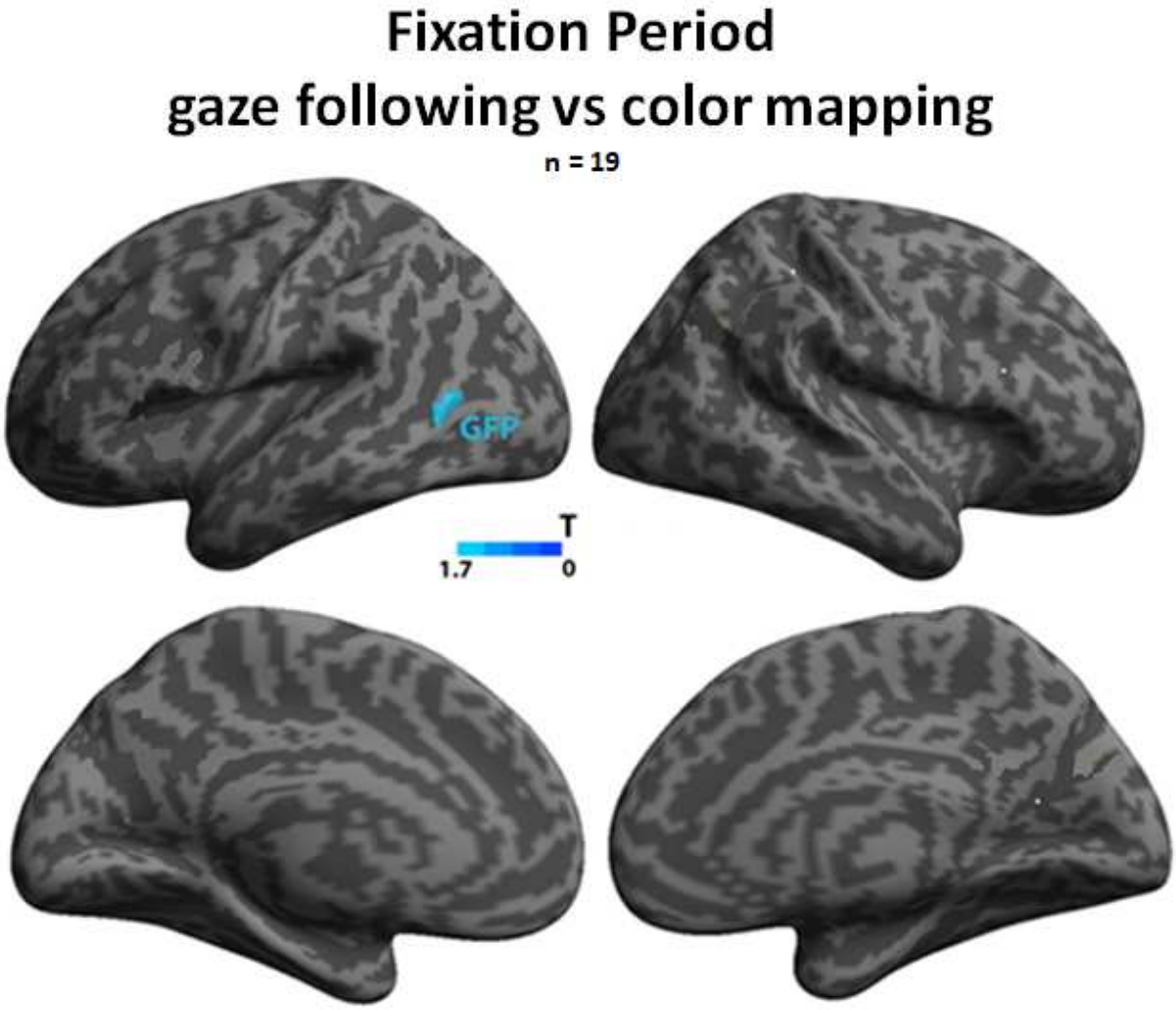

Figure 12: BOLD contrast during the fixation period between responses to the rule to perform gaze following and select a target based on eye gaze versus the rule to map the color of the eyes. A significant cluster for 'gaze following' versus 'color mapping' was found in the 'gaze following patch' (GFP) ($p<0.05$, uncorrected, cluster size: 5).

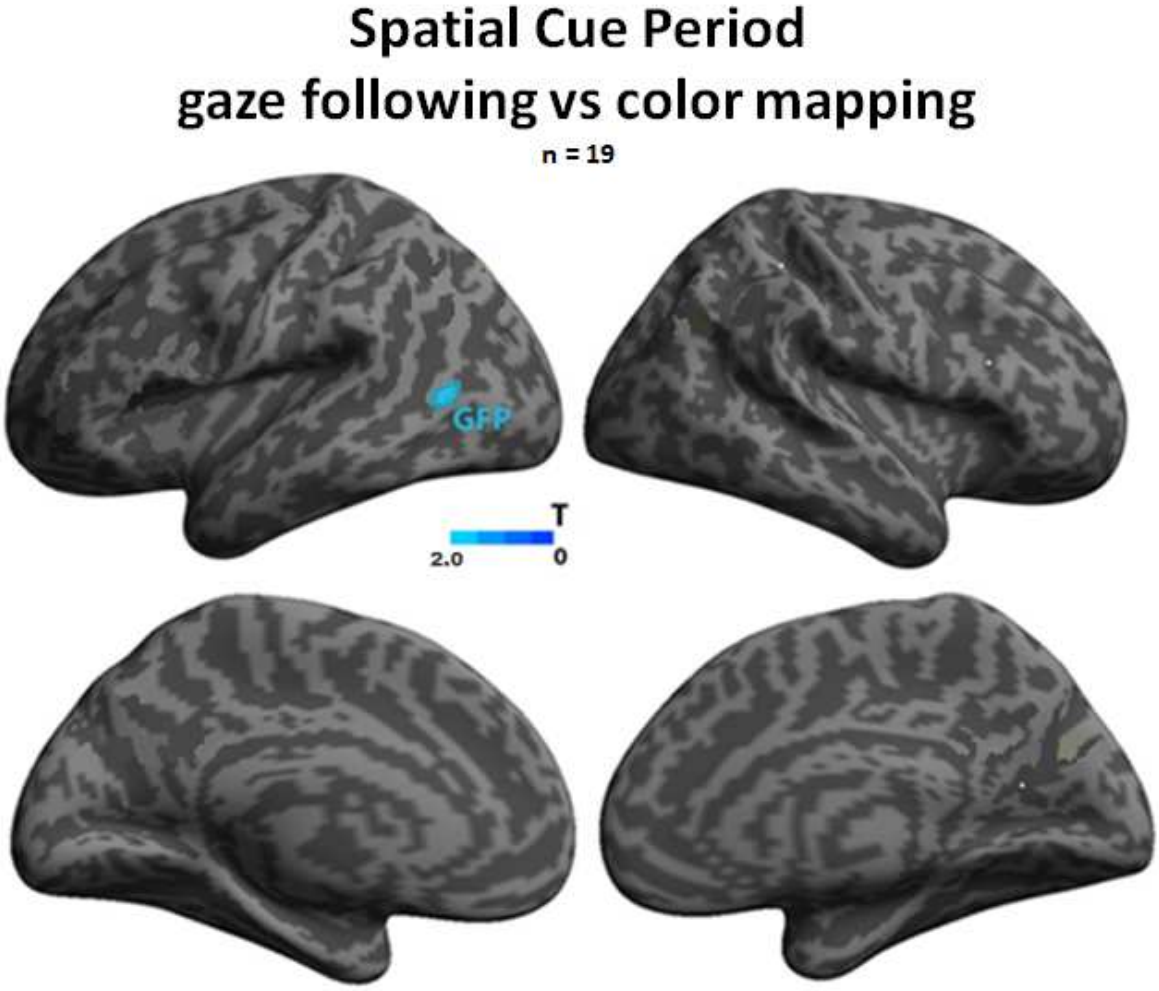

Figure 13: BOLD contrast during the spatial cue period between responses to the rule to perform gaze following and select a target based on eye gaze versus the rule to map the color of the eyes. A significant cluster for 'gaze following' versus 'color mapping' was found in the 'gaze following patch' (GFP) ($p<0.05$, uncorrected, cluster size: 5).

Area	Left	Right
dlPFC	-48 26 30	NA
OFC	-42 47 -05	NA
INS	-36 17 -10	NA
PPC	-33 -55 38	54 -52 35
precuneus	-03 -64 43	03 -64 38

Table 1: Peak MNI coordinate of areas implicated in cognitive control of gaze following (Contrast during the fixation period for 'color mapping' vs 'gaze following')
Abbreviations: dorsolateral prefrontal cortex (dlPFC), orbitofrontal cortex (OFC), insula (INS), posterior parietal cortex (PPC)

Area	Left	Right
dlPFC	-48 26 30	NA
PPC	-33 -55 38	Na
precuneus	NA	03 -64 38

Table 2: Peak MNI coordinate of areas implicated in cognitive control of gaze following (Contrast during the spatial cue period for 'color mapping' vs 'gaze following')
Abbreviations: dorsolateral prefrontal cortex (dlPFC), posterior parietal cortex (PPC)

3.3. Linear Correlation Analysis

To further test the hypothesis that the suppression of neural activation of the GFP in ‘color mapping trials’ is a consequence of the control of the frontoparietal network over the GFP, we performed a linear correlation analysis between the average beta values extracted from the GFP-ROIs and the two areas with maximum BOLD activity during color mapping trials i.e., the left dlPFC-ROI and the left PPC-ROI.

The analysis revealed a significant negative correlation between the GFP-ROI and the PPC (Spearman correlation, $p=0.03$, $r=-0.5$). Correlation between the GFP-ROI and the dlPFC-ROI was at the margin of significance (Spearman correlation, $p=0.05$, $r=-0.46$). This result suggests that the suppression of the GFP is indeed a consequence of inhibitory influence of the activation by frontoparietal areas.

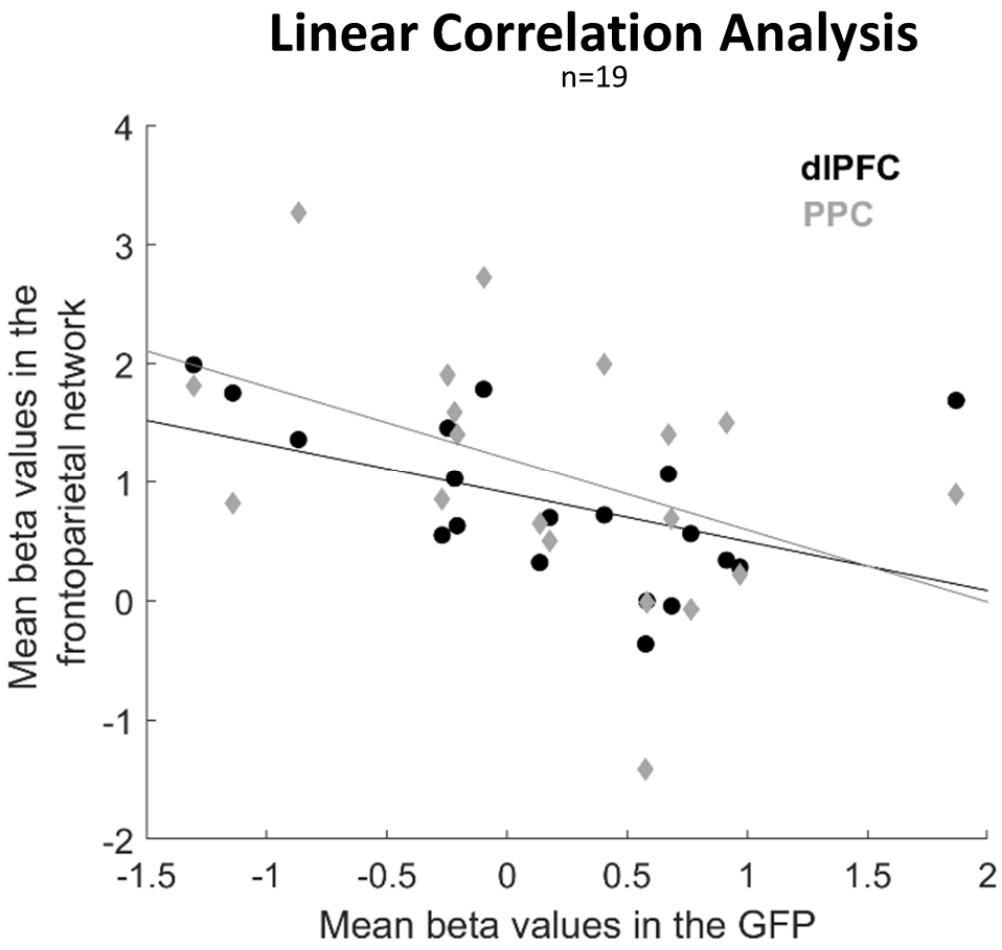

Figure 14: Linear correlation between mean beta values extracted from dorsolateral prefrontal cortex (dlPFC), posterior parietal cortex (PPC) and the 'gaze following patch' (GFP). There was a significant negative correlation between the GFP and the PPC (Spearman correlation, p=0.03, r=-0.5). Correlation between the GFP and the dlPFC was at the margin of significance (Spearman correlation, p=0.05, r=-0.46).

4. Discussion

In our current study we performed an fMRI experiment in order to identify cortical areas being activated related to the need to suppress gaze following. In the paradigm the need to suppress gaze following was implicated with the rule to perform an alternative gaze shift, a saccade driven by the instruction to localize a target in the peripheral visual field, corresponding to the eye color of the ‘sender’.

We could identify several frontal and parietal areas revealing an elevated BOLD response when gaze following needed to be suppressed. Among those are the dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex (PPC), but also the orbitofrontal cortex (OFC), insula and precuneus. We consider the first two to play the major part in this control network, since we were able to detect sustained activation in these areas apparent before as well as during the spatial cue period of our experiment. Additional authors also report on the dlPFC and PPC as the main actors of the frontoparietal control network (Dosenbach et al., 2007; Power et al., 2011; Yeo et al., 2011; Petersen et al., 2012), executing cognitive control among subordinated, executive areas to modulate human behavior in accordance to the needs of a given situation.

When it comes to the performance of gaze following, we could detect BOLD activation in a well-known temporal brain area. It is located in the posterior superior temporal sulcus (pSTS) and referred to as the ‘gaze following patch’ (GFP). Previous studies reported on the GFP being the neural substrate of gaze following in monkeys as well as in humans (Marciniak et al., 2014; Marquardt et al., 2017) and being involved in the geometric calculations to perform effective gaze following. In our study we could confirm these results and could also show that the study design we chose met our demands to specifically explore cognitive control in the context of gaze following.

4.1. A Frontoparietal Control Network for Deliberate Suppression of Gaze Following

4.1.1. Dorsolateral Prefrontal Cortex

We assume that the dlPFC controls consecutive areas to modulate behavior according to the needs of the given situation. In our experiment we detected BOLD signal change in the dlPFC when subjects received the instruction to perform a color matching trial and it was needed to suppress the execution of a saccadic gaze following.

The PFC is essential to exert cognitive control on subordinated areas to modulate behavior in accordance to the needs of a situation. Miller (2000) illustrates this role in a model where the PFC integrates different aspects, such as stimuli, internal goals and the current setting to choose form several possible responses. The same input stimuli would lead to different behavior given to different internal states such as context and motivation. Therefore, in context C1, being alone, stimuli S1 would lead to response R1, whereas in context C2, being among others, stimuli S1 would lead to response R2. To choose on the correct response, the PFC is interconnected with a wide range of neocortical areas, receiving projections from sensory areas and sending projections to motor and subcortical areas (Miller and Cohen, 2001). Especially BA 46 (part of the dlPFC) is interconnected to motor areas, not only to supplementary and pre-motor areas, but also to the frontal eye field, that allows the dlPFC to control gaze shifts. In our experiment where visual input had to be evaluated and gaze shifts had to be performed, the dlPFC is capable of both and could serve as an interface between input and output. It is able to choose from the different possible responses in accordance to the current internal state and to provide bias signals to consecutive brain areas to achieve a specific behavior in a top-down hierarchy (Miller et al., 2002).

To subdivide specific functions within the prefrontal cortex, Koechlin et al. (2003) performed an experiment and proposed a cascading model capable of stimuli, context and temporal episodes. The rostral lateral prefrontal cortex (BA

46) would evaluate information on episodic aspects, as for example previous events or ongoing internal goals. The caudal lateral prefrontal cortex (BA 9/44/45) would analyze the contextual input, in which the stimulus occurs and could control the execution.

Various studies report on activation in the dorsolateral prefrontal cortex for different aspects. Among those aspects are (working) memory (Barch et al., 1997; Koechlin et al., 2003; Ridderinkof et al., 2004), attentional selection (MacDonald et al., 2000; Banich et al., 2000; Rowe and Passingham, 2002), behavioral inhibition (de Zubicaray et al., 2000; Hwang et al., 2010) and reward expectation (Barraclough et al., 2004) (see Table 3). Within our experiment one might also argue that these aspects contribute to the BOLD activity we detected in dlPFC: Working memory reflecting the latest instruction, attentional selection to focus on the color of the iris instead of the direction of the gaze, behavioral inhibition not to perform the reflexive and automatic response of gaze following. Additional studies have shown that activity in the dlPFC is associated with the decision making process of goal directed behavior per se. Bunge et al. (2002) claim that the dlPFC is specifically involved in rule based selection of responses and also Schumacher et al. (2002) claim that activity in the dlPFC is specific to response selection, especially when various factors make a selection of the appropriate response more difficult. Finally, the authors conclude that BOLD activity in the dlPFC is associated with successful decision making and adapting behavior to the current demands of a task/situation. Taking this together, Miller and Cohen (2001) argue, all these aspects presented above (working memory, attentional selection, behavioral inhibition, reward expectation and also the decision making progress itself) cause activity in the dlPFC that is actually depending on the representation of goals and rules in the form of patterns of activity in prefrontal cortex. So ultimately all these aspects are subordinated to the overall goal, represented in the dlPFC. That leads to the conclusion that activity in the dlPFC is on the one hand reflecting the representation of the rule itself, on the other hand reflecting the rule based selection of the response. In our experiment BOLD activity in the dlPFC reflects cognitive control based on

the previously set rule and is providing bias signals modulating subordinated brain areas to execute the adequate behavior.

Furthermore, another aspect of the decision making progress in the dlPFC is that it seems to encode pay-offs, comparing expected pay-off and gained reward, which is essential for dynamic learning (Barraclough et al. 2004). This aspect also underlines the dlPFC's role in successful decision-making and goal-directed selection of appropriate responses.

To suppress gaze following subjects were instructed to ignore the gaze cue but instead perform a quite unnatural guided gaze shift. This is also congruent with one of the most fundamental aspects of cognitive control: the ability to select a weaker, in means of less automatic, but task-relevant response (Miller and Cohen, 2001) and to execute inhibitory control and suppress an inappropriate or incorrect response, although it might be the prepotent or even reflexive-like one (Aron et al., 2004; Bure et al., 2004). Badre et al. (2004) report on bilateral activity in the dlPFC, when a response had to be selected in the presence of a competing, and most important prepotent, in means of automatic, response. This can be illustrated for the classical Stroop task: prefrontal activity was detected when the color naming condition, the weaker response, needed to be executed over the prepotent and automatic, word-reading condition (MacLeod, 1991; MacDonald et al., 2000). Cognitive control is always needed, when automatic behavior represented by the `easy and familiar' neuronal pathways, cannot or should not be used to achieve a goal (Miller et al., 2002).

The situation we created in our experiment to suppress gaze following was not a simple do-not-task (do not perform gaze following), but a do-this-instead-task (perform a saccade depending on the 'color mapping rule'). So the question that might come up is, whether the activity found in the prefrontal cortex was in the first place caused by the means of the instruction and performance of color matching per se and not by the suppression of active gaze following. We cannot rule out this possibility, but if activity in the dlPFC would only reflect implementation of the specific instruction 'color mapping', each instruction (in

everyday life situation-response-association) would be in need of their own dedicated group of neurons encoding their specific meaning, instead of one group of neurons representing the abstract rule itself. The first solution would be a quite expensive one in means of number of needed neurons and it is way more efficient to encode an abstract rule (Miller et al., 2002). To distinguish the neural implementation of the 'color mapping rule' itself, one would have needed to use an additional control task, for example an identity-matching rule as used in gaze following studies in monkeys (Kamphius et al., 2009; Marciniak et al., 2014), to compare for rule specific differences.

We did not allow subjects to decide on their own to choose their behavior, but we gave them an instruction before each trial. One might argue that for our experimental setting the contextual aspect, the rule we set, predominates since subjects were not relying on internal goals and not 'choosing' among different responses. Our experimental design was not in the first place designed to answer the question of the circumstances where gaze following is suppressed in, whether by internal goals, contextual setting or external rules. We rather wanted to localize brain areas that are involved in the execution of a control function during gaze following and finally modulate behavior in accordance to the needs (external as well as internal) of a situation. Nevertheless, as elaborated above, contextual information and internal goals are often entangled in everyday life and both aspects are taken into account for the integration of cognitive control (Miller, 2000; Koechlin et al., 2003). Reviews from Miller and Cohen (2001), Miller et al. (2002) or Ridderinkhof et al. (2004) do not distinguish between externally or internally set rules/goals to evaluate the features of cognitive control. So both can be considered as different aspects of cognitive control, equally contributing, maybe even mutually dependent, to the decision making progress.

The role of the prefrontal cortex in cognitive control has been intensely explored and studies have focused on different aspects of control (see Table 3). The results from our current study can contribute an additional aspect of cognitive control: besides selecting a weaker but task-relevant stimulus and suppress the

prepotent, but inappropriate response (Miller and Cohen, 2001; Aron et al., 2004) it is even possible to execute control on an almost reflexive-like behavior (Burle et al., 2004). Gaze following is an essential part of non-verbal communication and indispensable for social interaction and so the gaze cue itself is a powerful stimulus. Several authors report on early, insuppressible shifts of attention, caused by head-gaze in monkeys (Marciniak et al., 2015) and eye gaze in humans (Friesen and Kingston,1998; Driver et al., 1999; Langton and Bruce, 1999) that could not be trigger by non-social directional cues (Jonides, 1981). We assume that the same is the case in our experiment: Early shifts of attention caused by eye-gaze cannot be suppressed, but the actual performance of gaze following can.

Function	Study
(Working) Memory	Milner, 1963
	Barch et al., 1997
	Koechlin et al., 2003
Attentional Selection	MacDonald et al., 2000
	Banich et al., 2000
	Rowe and Passingham, 2002
Behavioral Inhibition	de Zubicaray et al., 2000
	Hwang et al., 2010
Reward Expectation	Barraclough et al., 2004
Decision Making	MacDonald et. al., 2000
	Bunge et al., 2002
	Schumacher et al., 2002
	Badre et al., 2004

Table 3: Different studies on activity in dorsolateral prefrontal cortex associated with specific functions. Miller and Cohen (2001) claim all these aspects cause activity in the dlPFC that is actually depending on the representation of goals and rules.

4.1.2. Posterior Parietal Cortex

More recent studies agree on cognitive control not being executed by a single brain region but rather by largely not overlapping brain networks (Dosenbach et al., 2007; Marek and Dosenbach, 2015). Early studies on cognitive control stress the role of the anterior cingulate cortex (ACC) besides the dlPFC (Miller et al., 2002; Kerns et al., 2004; Carter et al., 2007). The most prominent model by Botvinick and colleagues (2001) proposes the ACC to monitor performance, to detect upcoming conflicts and to increase activity in the dlPFC if needed. More recent models proposed two anatomically and functionally distinct networks in cognitive control: the frontoparietal (FP) network, consisting of the dlPFC and posterior parietal cortex (PPC), especially the area around the intraparietal sulcus (IPS), and the cingulo-opercula (CO) network, including the dorsal anterior cingulate and bilateral frontal opercula (Dosenbach et al., 2007; Power et al., 2011; Yeo et al., 2011; Petersen et al., 2012).

Activity in the FP network is trial–associated, suggesting control initiation and implementing specific configurations of the task, considered as an adaptive execution of control, whereas activity in the CO network is considered as across-trial maintenance of the task-set and the overall representation of the goal, indicating a stable implementation of task mode and strategy (Dosenbach et al., 2007; Gratton et al., 2018). Notably sustained signals in the CO network are only present in cognitive demanding tasks compared to perceptually demanding tasks (Dubis et al., 2016).

Since our experimental design, an event-related paradigm, was in the first place aiming at detecting adaptive and transient activity elicited by the need to implement cognitive control, we were able to measure trial associated activity in FP network, but not in the CO network, which is in line with the current hypothesis of distinct functions in cognitive control of these two networks. Furthermore, relying on the excellent behavioral performance of our subjects in

both tasks we would not consider them as cognitively demanding and therefore do not expect them to elicit strong activity in the CO network.

The PPC is a rather large area also associated with integrating visual information and processing spatial information (Whitlock, 2017). Studies stress the importance of the PPC in detecting unexpected or relevant stimuli and facilitate goal-directed attention (Corbetta et al., 2000; Corbetta and Shulman, 2002; Fox et al., 2003). Nevertheless, most authors agree that control networks are clearly divided from attention networks (such as the dorsal and ventral attention network), although those do indeed contribute to additional aspects of cognitive control (Power et al., 2011; Vincent et al., 2008; Yeo et al., 2011; Petersen et al., 2012; Gratton et al., 2017). In this framework, prefrontal areas represent more abstract rules implicated in cognitive control while the PPC might represent more details of these instructions for example which spatial locations or features must be ignored (Brass et al., 2005).

Another possibility could be that the PPC activity is associated to performance during 'color mapping trials' monitoring, as proposed by Liston and colleagues (2006). While our task design does not allow to dissociate such possibly from suppression of gaze following-related activity, it is parsimonious to assume that the PPC might provide a compensatory signal in case that the dlPFC control signals are not strong enough to fully suppress gaze following related activity in the GFP. This notion gets further support from the fact that we found a negative correlation between the PPC and GFP signals in parallel to the negative correlation between the dlPFC and GFP signals. However, assuming that more color-rule-related BOLD activity in the PPC or dlPFC may reflect better cognitive control, one might expect to see fewer false decisions. Unfortunately, the number of error trials was too small to allow us to test if this prediction applied.

In our analysis we were only able to detect activity in left the dlPFC and more accentuated activity in the left PPC. Several studies report on asymmetries within the FP network, showing that the left and right FP network have different patterns in timing and are related to distinct processes in cognitive control. The

left FP showed early onset activity, associated with cue response and strong target activation, peaking at the time point of decision making, whereas the right FP showed delayed and prolonged activity, suggesting response evaluation and adjustment (Gold et al., 2007; Gratton et al., 2017). This is in line with our results on early activity in left FP network, arising at and even before the early spatial cue period in advance to the time point of decision making and behavioral execution.

4.1.3. The ‘Gaze Following Patch’ in pSTS

The context of cognitive control we were interested in for our experiment was a very specific setting that occurs in everyday life. The neural substrate of gaze following has been intensely evaluated in the past and was located in a specific area in the posterior superior temporal sulcus: the ‘gaze following patch’ (GFP). This area is present in monkeys (Marciniak et al., 2014) as well as in humans (Materna et al., 2008; Marquardt et al., 2017). Also in our study we were able to detect BOLD activity in superior temporal sulcus when subjects performed gaze following. Furthermore, our results suggest that the frontoparietal control network is executing control by directly interfering on the level of the GFP to suppress gaze following. This could be shown in the negative linear correlation of activity in the dlPFC/PPC and GFP, when high activity in the dlPFC/PPC was correlated with reduced activity in the GFP.

The extraordinary value of eyes and eye gaze in social interaction is due to a complex communication system that is relying on information contained within the eyes (Andrew, 1963; Emery, 2000). To detect where a counterparts attention is directed all primates take into account several hints such as eye gaze, head direction and body orientation. If those hints are incongruent, eye gaze is considered to provide the most important information and will ouverrule directional cues from additional body parts (Perrett et al., 1992). Langton et al. (2000) propose the STS region is not only selectively sensible to the perception of gaze (Allison et al., 2000), but even containing a neuronal system exclusively

dedicated to the processing of gaze direction. Furthermore, since gaze following is indispensable for learning (Mineka et al., 1984; Dunham et al., 1993; Munday et al., 1998) and efficient social interaction (Baron-Cohen, 1994/1995b; Emery, 2000; Liuzza et al., 2011) various studies explored the neural substrates of gaze perception and gaze following and could locate a dedicated area in the posterior parts of the superior temporal sulcus (pSTS) in humans (Puce et al., 1998; Hoffmann and Haxby, 2000; Hooker et al., 2003; Pelphrey et al., 2004; Materna et al., 2008; Marquardt et al., 2017) (see Table 4).

In our study we also detected BOLD activity in the STS region. Compared to previous studies the area we detected activity in was located more medial, but still being part of the superior temporal sulcus. Interindividual differences might cause this discrepancy. Another aspect that needs to be taken into account is the fact that our experimental design was not primarily aiming at the detection of activity caused by gaze following, but at the detection of cognitive control. Therefore we used an event-related design instead of a block design as previous studies did. The activity we detected in the pSTS was quite low and only located in the left hemisphere, probably due to the lower statistical power of the event-related design compared to a regular block design. Nevertheless, being able to detect BOLD activity in this well-defined region confirms that the task design we chose would meet our demands to study cognitive control in the context of gaze following.

In our experiment subjects were not able to choose whether to perform or to suppress gaze following. Claiming that gaze following is an almost reflexive-like behavior and choosing a design when it has to be performed after a go-signal seems to be a contradiction. Even though the experimental design does not reflect natural behavior, it is well established and was used in several studies before, in monkeys as well as in humans, to investigate the neural substrates of gaze following (for example: Materna et al., 2008; Kamphius et al., 2009; Marciniak et al., 2014; Marquardt et al., 2017).

Since gaze following is such an essential part of non-verbal communication and social interaction, it is not only necessary to be performed in a very fast and precise way (Bock et al., 2008), it is also necessary to be flexible and adaptable. Human behavior is complex and guided by numerous influences. To be able to adapt behavior to the special needs of a situation, it also includes to overrule a reflexive-like behavior if necessary (Burle et al., 2004). We could show that this is also the case for gaze following. When cognitive control processes are in charge, activity in the GFP is suppressed by bias signals form the FP control network, executing inhibitory control in a top-down manner on reflexive-like behavior.

Study	Location	Hemisphere	BA (Brodmann area)	Coordinates Talairach
Puce et al. (1998)	STS	R	22	47 -53 07
	STS	R	22	49 -49 03
	MTG	L	21	-49 -48 03
	MTG	L	39	-46 -53 05
Hoffman and Haxby (2000)	MTG	R	37	50 -63 04
	MTG	L	39	-45 -56 11
	STS	L	22	-56 -48 08
Hooker et al. (2003)	STS	R	22	50 -45 16
	STS	L	19	-49 -61 16
Pelphrey et al. (2004)	STS	R	22	55 -45 12
Maternal et al. (2008)	MTG	R	37	52 -62 10
	MTG	L	37	-52 -60 11
Marquardt et al. (2017)	MTG	R		50 -64 02
	MTG	L		-54 -67 06

Current study	**STS**	**L**	**22**	**-51 -61 03 (MNI)**

Table 4: Activation clusters of different studies on gaze perception and gaze following.
The activity we detected in our experiment during gaze following was located more medially compared to the results of these studies, but still being located at the superior temporal sulcus.
Abbreviations: middle temporal gyrus (MTG), superior temporal sulcus (STS)

4.2. Additional Areas

4.2.1. Orbitofrontal Cortex and Precuneus

In our experiment we also detected activity in the left orbitofrontal cortex (OFC) as well as in bilateral Precuneus before gaze following had to be suppressed. As elaborated above, both areas are considered to contribute to the process of gaze following, joint attention and creating a Theory of Mind (ToM) which are viable aspects of social interactions.

Besides the STS-Region, the orbitofrontal cortex and amygdala are considered to be the main actors in this context. Several PET studies stress the important contribution of these areas in social cognition especially when gaze monitoring is required (Kawashima et al., 1999; Wicker et al., 2003). The STS is gaining visual information and forwarding to the amygdala and OFC, which are key players in social cognition (Wicker et al., 2003). The amygdala and OFC are considered to add emotional value and social relevance to those stimuli, i.e. eyes, faces and bodies (Emery, 2000).

Additionally, we could also detect activity in the precuneus before and whilst gaze following needed to be suppressed. The precuneus is especially involved in taking in third-person perspective (Vogeley et al., 2004), which is essentially needed to understand other people's actions and intentions. Farrow et al. (2001) performed an fMRI experiment and detected activity in the precuneus during judgments that required empathy. More importantly, Vogeley et al. (2004) even reported on activity in the bilateral precuneus during first- as well as third-person perspective and concluded that both seem to base on common neuronal functions in the bilateral precuneus.

In our experiment we detected activity in the OFC and precuneus before gaze following had to be suppressed. We think this is due to the fact that gaze direction is a potent social stimulus and although it is possible to inhibit gaze shifts by suppressing gaze following, the perception of gaze as stimuli would

still lead to consecutive activation in cortical areas being involved in detection and evaluation of gaze and its social/contextual relevance.

4.2.2. Anterior Insula

We also found task-related BOLD signals in the left anterior insula in ‘color mapping trials’. This region has previously been associated with many functions including interoception (Critchley et al., 2004; Barrett et al., 2004), awareness of body movements (Farrer et al., 2002), speech processing (Ackermann and Riecker, 2004), visual and auditory awareness (Kondo et al., 2007; Pressnitzer et al., 2006) and attention (Weissman et al., 2006; Mason et al., 2007). Furthermore, the anterior insula is considered to be detecting salient stimuli which capture attention (Uddin et al., 2005) and therefore to be part of the salience network, consisting of the ACC, ventral anterior insula, as well as subcortical and limbic areas (Seeley, et al., 2007; Power, et al., 2011).

In our experiment we detected BOLD activation in the anterior insula in trials when gaze following had to be suppressed. We think this is due to the insula’s involvement in the salience network and its function of guiding attention and visual awareness to capture the correct stimulus. We detected this BOLD activation before the spatial cue became available and consider it as a primary preparatory signal in expectation of the upcoming stimuli.

4.3. Design and Statistics

For the conception of our experiment we decided on a mixed block and event-related design for several reasons. First we hoped to be able to distinguish between sustained and transient cognitive control signals, if existent. Braver et al. (2003) proposed a design model we used as scheme and modified for our purpose. Second for the detection of prefrontal activity we needed a sufficient number of task switches. We therefore focused on the event-related part and subjects performed three times as many trials in the event-related part than in the blocks.

We hoped that through comparing brain activity during 'color mapping trials' presented in blocks and 'color mapping trials' presented event-related we could distinguish between sustained and transient aspects of cognitive control. Therefore we added a 5 seconds delay between the trials in the block design that would correspond to the 1-5 seconds delay between the task instruction and the fixation picture in the event-related design to allow us to compare these two settings. But the number of trials in blocks was very low, each subject only performed 15 trials for a color block so that the statistical significance was negligible and we mainly focused on the analysis of event-related trials.

As for the statistical power of an event-related design, Friston et al. (1999b) point out that for statistical aspects the most efficient design is still a conventional block design. Nevertheless considering that the most efficient design for one effect may not be the most efficient for another and because we were interested in brain activity most likely associated to task switching, we still chose an event-related design.

The statistical power to capture cognitive control signals was very high ($p<0.01$, FDR-corrected, cluster size: 20).), but for the underlying gaze activity we could not use common thresholds. We think this is still justifiable since our paradigm was inspired by previous studies on gaze following and the activity we captured during 'gaze following' is located in a well-known area in the pSTS that is even referred to as the 'gaze following patch'. Furthermore, we added an additional

correlation analysis to support our hypothesis that could reveal a negative correlation between the frontoparietal areas and the GFP. We think that the combination of BOLD response and linear correlation are finally strengthening the reliability of our results.

4.4. Conclusion

In our fMRI-experiment we could identify brain regions with suppression-related BOLD activity including dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex (PPC) as its main foci. Activation of this network led to the suppression of the activation in the ’gaze following patch’ (GFP), an area previously shown to be essential in social gaze following behavior. The suppression of gaze following most probably involves the generation of a veto-signal among those networks, conveyed to the GFP and other dependent cortical structures. Our study suggests that the frontoparietal control network is involved in the control and supervision of gaze following by integrating contextual information for the suppression of gaze following in situations in which it may be inappropriate to follow the gaze of others.

5. Abstract

In humans, the face and the eyes are major sources of information on the other´s mental and emotional state. Gaze following is an essential part of nonverbal communication and indispensable for successful social interaction. It is the direction of gaze that informs us about objects another person might be interested in. By following the other's gaze to this object, we are able to establish 'joint attention'. And by mapping our own object-associated needs, interests and aspirations onto the other, we develop a Theory of her/ his Mind (ToM). Human gaze following is a fast and almost reflex-like behavior, yet, it can be controlled and suppressed if it seems to be inappropriate in a situation. As shown by fMRI studies, the major substrate of human gaze following is a well circumscribed region in the posterior superior temporal sulcus (pSTS), the so called 'gaze following patch' (GFP). In order to identify the properties and define the cortical substrate of cognitive control in gaze following, we carried out an fMRI experiment, in which human subjects were exposed to gaze cues which, depending on the prevailing instruction, were used to perform a gaze following action or an equivalent gaze shift. In detail, the subjects saw the portrait of a female, the 'sender', looking with her eyes at one out of five targets in front of her. Subjects had to follow the gaze of the sender with a saccade to the target ('gaze following'). Alternatively, they had to ignore the gaze and had to look at the target matching the sender´s (variable) eye color ('color mapping'). The two trial types were presented in an even- related design, the tasks being randomly interleaved.

In our experiment we could identify BOLD activity in several frontal and parietal brain areas related to the rule to suppress gaze following by mapping eye color. In order to have enough time to act on the reflexive gaze following responses in 'color mapping trials', we reasoned that the neural state representing the preparatory rule must be established before the actual spatial cue became available. Hence, we looked at the BOLD responses at a time window of 5 sec before the appearance of the task picture. Significant prefrontal activation was found in left frontal cortex including dorsolateral prefrontal cortex (dlPFC),

orbitofrontal cortex (OFC) and the insula. We also found activity in the left and right posterior parietal cortex (PPC) and bilateral precuneus. In accordance with previous works on gaze following we also detected activity in the GFP in left pSTS region when subjects were instructed to performed gaze following. For further analysis we added a linear correlation analysis that revealed a significant negative correlation between PPC and GFP and a negative correlation between dlPFC and GFP at the margin of significance.

In sum, these results are indicating that the frontoparietal control network executes an inhibitory influence on GFP when gaze following needed to be suppressed. Therefore it is integrating contextual information and modulating human behavior in accordance to the needs of a given situation.

6. Zusammenfassung

Die Augen sind ein elementarer Bestandteil nonverbaler Kommunikation. Sie können uns Hinweise auf das Innerste eines Gegenübers, seine Gedanken und Gefühle geben. Wenn sich der Blick des Gegenübers in eine bestimmte Richtung wendet, enthüllt er Informationen über dessen Interessen, Wünsche und Bedürfnisse. Folgen wir diesem Blick (Blickfolgereflex oder gaze following) und lenken unsere eigene Aufmerksamkeit auf denselben Gegenstand, erzeugen wir den Zustand der gemeinsam gerichteten Aufmerksamkeit (joint attention). Übertragen wir, in einem nächsten Schritt, unsere eigenen objektbezogenen Wünsche und Bedürfnisse auf das Gegenüber, erschaffen wir so eine Hypothese bezüglich seiner Gedanken und Absichten (Theory of Mind - ToM). Der menschliche Blickfolgereflex ist schnell, präzise und automatisch, doch wie jedes menschliches Verhalten muss auch er flexibel und anpassungsfähig sein. So ist es uns im alltäglichen Leben möglich, diesen Blickfolgereflex zu unterdrücken wann immer es uns in einer Situation unangebracht erscheint oder wir beispielsweise unsere eigenen Absichten verbergen wollen.

Vorangegangene fMRT-Studien haben sich bereits intensiv mit dem Blickfolgereflex und seinen neuronalen Grundlagen auseinandergesetzt. Diese konnten zeigen, dass ein Areal im posterioren superioren temporalen Sulcus (pSTS), der so genannte ‘gaze following patch’ (GFP), für seine korrekte geometrische Ausführung verantwortlich ist. In unserem Experiment wollten wir übergeordnete Hirnstrukturen identifizieren, die eine Kontrollfunktion auf dieses Areal ausüben und situationsabhängig den Blickfolgereflex modulieren und unterdrücken können. Dazu haben wir ein fMRT-Experiment an 20 Probanden durchgeführt, die in diesem Kontext zwei verschiedene Aufgaben zu lösen hatten. Im Experiment wurde ein Aufgabenbild präsentiert, auf dem ein weibliches Gesicht zu sehen war, der sogenannte ‘Sender’, der abwechselnd auf eines von fünf Zielobjekten blickte, die in einer horizontalen Linie im Vordergrund angeordnet waren. Gleichzeitig konnte sich auch die Augenfarbe des Senders ändern, sodass diese mit einer der (unterschiedlichen) Farben der Zielobjekte übereinstimmte. Für die Aufgabenstellung ‘Blickverfolgung’ (‘gaze following’) sollten Probanden der Blickrichtung des Senders folgen und eine Sakkade zum selben Zielobjekt vollführen, in der zweiten Aufgabenstellung ‘Farbverfolgung’ (‘color mapping’) sollten Probanden die Blickrichtung ignorieren und eine Sakkade zum Zielobjekt in derselben Farbe ausführen. Die beiden Aufgabentypen wurden randomisiert und die Probanden vor jedem Durchgang instruiert, welche der beiden Regeln anzuwenden ist.

Unter der Annahme, dass kognitive Kontrollprozesse zur Unterdrückung eines reflexähnlichen Verhaltens eine gewisse Vorlaufzeit benötigen, konzentrierten wir uns in unserer Auswertung auf einen Zeitpunkt 5sec vor Erscheinen des Aufgabenbildes. Für die Unterdrückung des Blickfolgereflexes konnten wir BOLD-Aktivität in mehreren frontalen Arealen detektieren. Bei diesen handelt es sich um den dorsolateralen präfrontalen Cortex (dlPFC), den orbitofrontalen Cortex (PFC) und die Inselrinde. Daneben zeigte sich neuronale Aktivität im rechten und linken posterioren Parietalcortex (PPC) und bilateral im Precuneus. Waren die Probanden instruiert worden eine Blickverfolgung auszuführen, konnten wir BOLD-Aktivität im linken posterioren superioren Temporalsulcus (pSTS), im sogenannten ‘gaze following patch’ (GFP), nachweisen. Zur

weiteren Analyse ergänzten wir eine lineare Korrelation, hier zeigte sich eine signifikante, negative Korrelation zwischen PPC und GFP, so wie eine negative Korrelation zwischen dlPFC und GFP an der Grenze zur Signifikanz.

Insgesamt konnten wir mit unseren Ergebnissen zeigen, dass das frontoparietale Kontroll-Netzwerk einen hemmenden Einfluss auf den GFP ausüben kann, um so den Blickfolgereflex zu unterdrücken. Hierbei werden situationsabhängige Informationen berücksichtigt und das menschliche Verhalten situativ angepasst.

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8. Erklärung zum Eigenanteil der Dissertationsschrift

Die Arbeit wurde im Hertie-Institut für klinische Hirnforschung unter Betreuung von Prof. Dr. Hans-Peter Thier durchgeführt.

Die Konzeption der Studie erfolgte in Zusammenarbeit mit Dr. Peter W. Dicke, postdoc, und Hamidreza Ramezanpour, Ph.D. student.

Sämtliche Versuche wurden von mir in Zusammenarbeit mit Dr. Peter W. Dicke durchgeführt.

Die statistische Auswertung erfolgte nach Anleitung und in Zusammenarbeit mit Hamidreza Ramezanpour durch mich.

Ich versichere, das Manuskript selbständig verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben. Alle wörtlich oder inhaltlich übernommenen Stellen habe ich als solche gekennzeichnet.

Tübingen, den 23.03.2021

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Unterschrift