

INDEPENDENT MAX PLANCK RESEARCH GROUP FOR SOCIAL NEUROSCIENCE AT
THE MAX PLANCK INSTITUTE OF PSYCHIATRY

**Social cognition and behavioral responses
in kinematic interactions -
neuroscientific evidence from a third-
and second-person perspective**



DISSERTATION
ZUM ERWERB DES DOCTOR OF PHILOSOPHY (PH.D.)
AN DER MEDIZINISCHEN FAKULTÄT DER
LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

vorgelegt von
Imme Christina Zillekens

aus
Aachen, Deutschland

am
27. November 2019

Supervisor:	PD. Dr. Leonhard Schilbach
Second expert:	Prof. Dr. Nikolaos Koutsouleris
Dean:	Prof. Dr. med. dent. Reinhard Hickel
Date of oral defense:	28. February 2020

Abstract

As social beings, humans are constantly probed to infer intentions from verbal and non-verbal communication and to react according to the kinematic signals of other people. In this way, social cognition is tightly bound to our ability to perceive, predict and perform socially relevant actions. Being characterized by impairments in social interactions, individuals with autism spectrum disorder (ASD) demonstrate insensitivity to predictive social stimuli as well as abnormal kinematic control both on the behavioral and the brain level. Underlining the severe consequences of impaired social interactive capabilities, autistic individuals are at high risk of social exclusion and concomitant mental health issues. Therefore, the investigation of the behavioral and brain responses to social actions might yield valuable insights into the fundamental dynamics of social interactions, which could lay the foundation for clinical research and interventions in ASD. In order to provide first insights, the main goal of this thesis was to identify the non-pathological brain mechanisms in perceptual action prediction and action control within a social context.

For this purpose, two functional magnetic resonance imaging (fMRI) experiments in healthy control participants were conducted: The first study of this thesis addressed the effect of observing communicative, i.e. predictive, actions on visual perception [*interpersonal predictive coding (IPPC)*]. By the use of point-light displays, we replicated behavioral findings of improved visual discriminability of a point-light agent after seeing a communicative as compared to an individual action of another point-light agent. Furthermore, our findings suggest a perceptual integration of social event knowledge implemented by the superior frontal gyrus (SFG) during predictive trials and a specific role of the amygdala in setting network configurations to meet the demands of the specific social context. Moving from a spectator perspective to direct involvement in a social interaction, the second study of this thesis examined the interaction of gaze processing and action control during an encounter with an anthropomorphic virtual character. The key finding of this second study comprises an increased functional coupling during high action control demands between the right temporoparietal junction (TPJ) as central gaze processing region and brain areas implicated in both action control processes and social cognition such as the inferior frontal gyri.

The results of the two studies demonstrate that predictive social actions as well as direct gaze signals can modify multimodal functional integration in the brain, thereby recruiting and modulating activation in brain structures implicated in ASD. In this way, the two studies of this thesis underline the interdependence of social cognition and kinematic processes while providing a reference point for future studies on ASD.

Abbreviations

ADHD attention deficit hyperactivity disorder

AQ Autism Quotient

ASD autism spectrum disorder

BOLD blood oxygenation level dependent

EEG electroencephalography

fMRI functional magnetic resonance imaging

IFG inferior frontal gyrus

fNIRS functional near-infrared spectroscopy

IPPC interpersonal predictive coding

MEG magnetoencephalography

mPFC medial prefrontal cortex

MTG middle temporal gyrus

ROI region of interest

RT reaction time

SFG superior frontal gyrus

TAC thesis advisory committee

tDCS transcranial direct current stimulation

TMS transcranial magnetic stimulation

TPJ temporoparietal junction

ToM Theory of Mind

TR repetition time

Contents

Abstract	i
Abbreviations	iii
1 Introduction	1
1.1 Access to others' minds through social action signals	1
1.2 Translational perspective on social kinematics: the case of ASD	3
1.3 Perception & prediction based on communicative actions	5
1.3.1 From action observation to social cognition	5
1.3.2 Communicative actions and visual perception	6
1.3.3 Investigating IPPC by means of point-light displays	7
1.3.4 IPPC in a nutshell	8
1.4 Motor control in a social context & from a second-person perspective	8
1.4.1 Direct gaze as communicative signal conveying the intentions of another person	8
1.4.2 Neural correlates of gaze processing	9
1.4.3 Gaze and action control	10
1.4.4 Face-to-face: third- vs. second-person perspective	11
1.4.5 Résumé: direct gaze and action control from a second-person perspective	12
1.5 Aims of the thesis	13
2 Perception of Social Kinematics	15
2.1 Summary	15
2.2 Contributions and reference	16
2.3 Increased functional coupling of the left amygdala and medial prefrontal cortex during the perception of point-light displays	17
3 Direct Gaze and Action Control	29
3.1 Summary	29
3.2 Contributions and reference	30

| CONTENTS

3.3	A look at actions: Direct gaze modulates functional connectivity of the right TPJ with an action control network	31
4	Discussion	43
4.1	The neural and behavioral correlates of IPPC	43
4.1.1	Communicative signals shape visual perception	43
4.1.2	IPPC builds on social knowledge	44
4.1.3	The role of the amygdala in adapting to a predictive or non-predictive context	45
4.1.4	Methodological considerations	46
4.2	Gaze processing and action control	46
4.2.1	The direct gaze effect and autistic traits	47
4.2.2	Incongruency costs reflected in connectivity of the right TPJ	47
4.2.3	The role of the follower and implicit mentalizing	48
4.2.4	Action control beyond imitation and beyond social cues	49
4.2.5	Experimental design and potential modifications	49
4.3	General discussion and outlook	50
4.3.1	fMRI: valuable approach despite methodological limitations	50
4.3.2	From a third- to a second-person perspective	51
4.3.3	Towards a psycho-behavioral BOLD endophenotype	52
4.3.4	Interventions	54
4.4	Conclusions	55
	Bibliography	57
	Acknowledgments	71
	Publications	73

1 Introduction

1.1 Access to others' minds through social action signals

In the course of evolution, humans have evolved as prematurely born, altricial beings whose brain development is considerably impacted after birth – by the social world around them (Coqueugniot, Hublin, Veillon, Houët, & Jacob, 2004; Shultz, Klin, & Jones, 2018). Representing about one third of its adult brain size at birth (Holland et al., 2014), the human brain undergoes periods of extensive growth followed by synaptic pruning, i.e. the elimination of unused synaptic connections between neurons, thereby opening a window of experience-based brain plasticity that interacts with genetic predispositions (Greenough, Black, & Wallace, 1987; Huttenlocher, 1990). It has further been shown that brain regions associated with empathy and mentalizing, i.e. making inferences about another person's thoughts and feelings (Adolphs, 2009; Schilbach et al., 2013), are sensitive to the individual history of interactive experiences (Johnson, 2005; Levy, Goldstein, & Feldman, 2019; Senju & Johnson, 2009a). In this way, our lives depend on and our social cognitive development is shaped by the experiences with others.

Importantly, social cognition has been tightly linked to the kinematic elements of social interactions (Cook, 2016; Yang, Rosenblau, Keifer, & Pelphrey, 2015). More specifically, action observation as well as the active, motor-driven participation in social interactions, starting early on in life, have been described as fundamental processes that enable humans to develop social cognitive abilities (Carpenter, Nagell, & Tomasello, 1998; Rendell et al., 2010; Schilbach et al., 2013). Alluding to the neural interdependency, action observation, action execution and action understanding have been described as inseparable neural processes that are “[...] bridged through shared, abstract conceptual representations [...]” (Caramazza, Anzellotti, Strnad, & Lingnau, 2014, p. 11). Following up on these lines, experience and expertise with an observed action has been linked to the accuracy of the interpretation of the action as well as the prediction of action outcomes (Aglioti, Cesari, Romani, & Urgesi, 2008; Casile & Giese, 2006; Cook, 2016; Kilner, Hamilton, & Blakemore, 2007). For the latter, communicative actions such as gestures (Figure 1A) or gaze movements (Figure 1B) represent important social signals that allow inferences on the intentions of the acting agent (Becchio, Manera, Sartori, Cavallo, & Castiello, 2012; Manera, Schouten, Becchio, Bara, & Verfaillie, 2010; Senju & Johnson, 2009a). Thus, by “reading” interactive actions, we are developing a metacognitive theory about another person's mind in our own mind [*Theory of Mind (ToM)*]. Reversely, ToM might in turn be necessary for action control processes in dissociation of the intentions of the other person (Brass, Ruby, & Spengler, 2009).

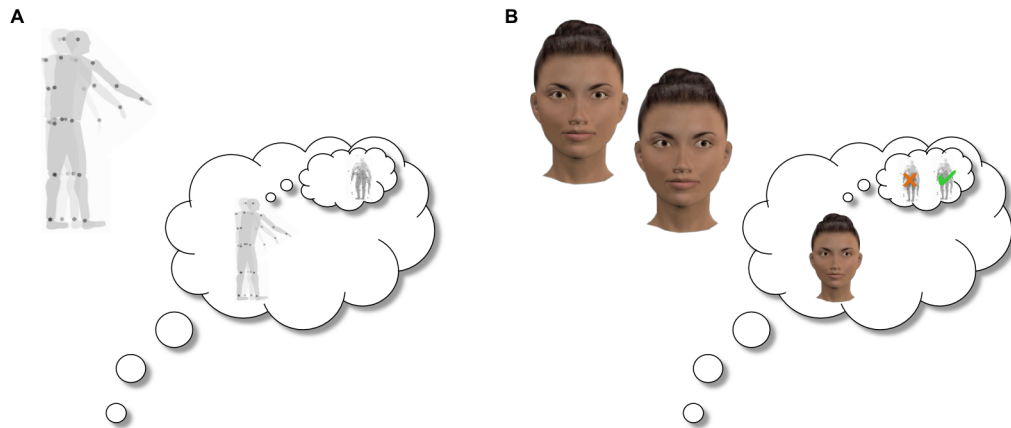


Figure 1. *Examples of mentalizing triggered by social kinematic signals.* (A) A communicative action might inform the observer's theory about the intentions of the observed agent. In this case, the observer predicts the agent to expect a second agent to perform a complementary response action. (B) Initiating a social interaction by direct gaze, the observer becomes an interaction partner. Based on the gaze shift of the virtual character, the interaction partner automatically hypothesizes on which side the virtual character wants to seat the interaction partner. [Point-light agents obtained from the Communicative Interaction Database (Manera et al., 2010; Manera, Del Giudice, et al., 2011); virtual character created in Poser 10 (Smith Micro Software, Inc., CA, USA) by L. M. Schliephake]

Social metacognition has been subdivided into explicit and implicit ToM (C. D. Frith & Frith, 2012). While explicit ToM could be consciously trained and prompted, the concept of implicit mentalizing refers to automatic or unconscious processes (C. D. Frith & Frith, 2008) that have been associated with spontaneous kinematic alignment between two agents, forming a social unit (K. L. Marsh, Richardson, & Schmidt, 2009). Correspondingly, empathetic perspective-taking capacities have been related to the individual's degree of behavioral adaptability (Chartrand & Bargh, 1999). Critically, the ability or inability to socially align and behave in a normative, socially accepted manner has an impact on an individual's social integration or acceptance. Empirical evidence shows that behavioral synchrony and imitation as well as shared experiences lead to more positive judgements of another person, increased interpersonal affiliation and positive affect (Chartrand & Lakin, 2013; Hove & Risen, 2009; Kirsch, Drommelschmidt, & Cross, 2013). Reciprocity in social interactions as compared to one-directional communication is further known to elicit an increased blood oxygenation level dependent (BOLD) response in the reward system of the brain (Alkire, Levitas, Warnell, & Redcay, 2018; Pfeiffer et al., 2014). On the other hand, violations to social norms might lead to neurovascular error signals and subsequent behavioral adaptations of the perpetrator (Klucharev, Hytönen, Rijpkema, Smidts, & Fernández, 2009). Further, driven by negative affect and the perception of social unfairness, the pursuit of social alignment becomes apparent when considering that humans are even willing to make decisions that are harmful to themselves in order to punish social misconduct (Fehr & Fischbacher, 2004). In this sense, non-aligned individuals, lacking access to the minds of others via social actions, might be subject to societal

exclusion, which will be addressed in the following section by looking at the specific case of autism spectrum disorder (ASD).

1.2 Translational perspective on social kinematics: the case of ASD

ASD is a developmental condition that is characterized by impairments in social interaction and communication as well as restricted interests and repetitive behaviors (American Psychiatric Association, 2013; Asperger, 1944; Kanner, 1943). The prevalence of the psychiatric condition is estimated at 1-1.5% in the general population (Blaxill, 2004; Brugha et al., 2011; Glerean et al., 2016; Sun et al., 2019). While affected individuals often suffer from hyper- or hyporeactivity to sensory input (Marco, Hinkley, Hill, & Nagarajan, 2011) and might have intellectual disabilities (DeMyer, Hingtgen, & Jackson, 1981), the Ancient Greek meaning of the term “autism” (“autos”, self) refers to the increased risk of being socially isolated as compared to matched peers, which is driven by both social exclusion and self-withdrawal (Coleman-Fountain, 2017; Müller, Schuler, & Yates, 2008; Orsmond, Shattuck, Cooper, Sterzing, & Anderson, 2013; White & Roberson-Nay, 2009). This bilateral social isolation becomes apparent in everyday socially demanding contexts such as the working environment, where autistic individuals have named social expectations and interactive demands as the core stress and load factors (Kirchner & Dziobek, 2014). Correspondingly, epidemiological studies in German and US American cohorts have reported every second to third autistic adult, notwithstanding high educational levels, to be unemployed (Frank et al., 2018; Howlin & Magiati, 2017; Kirchner & Dziobek, 2014).

Despite an estimated heritability of approximately 90% (Freitag, 2007; Ronald & Hoekstra, 2011), environmental effects are known to interact with genetics, additionally influencing the position on the autistic spectrum and therefore, potentially mitigating autistic symptoms and impacting the individual's trajectory (Muhle, Trentacoste, & Rapin, 2004; Santangelo & Tsatsanis, 2005). In this sense, societal inclusion has been related to increased life satisfaction (Schmidt et al., 2015) and positive developmental trajectories in autistic children (Woodman, Smith, Greenberg, & Mailick, 2016). By contrast, it has been argued that repeated negative experiences during social interactions in early infancy potentiate to foster psychosocial stress, which negatively correlates with the level of social functioning (Bishop-Fitzpatrick, Mazefsky, Minshew, & Eack, 2015). Moreover, unemployment and social isolation have been identified as risk factors for comorbid psychiatric diseases (Albantakis, Parpart, Thaler, et al., 2018; Müller et al., 2008). Corresponding to the aforementioned social implications, major depressive disorder as well as social anxiety disorder embody the two most common comorbidities, affecting one to five in 10 autistic individuals (Albantakis, Parpart, Krankenhagen, et al., 2018; Hofvander et al., 2009; Howlin & Magiati, 2017). Further stressing the need for (early) clinical interventions, aggression, deliberate self-injuries and suicidal attempts are common behavioral expressions of ASD (Lai, Lombardo, & Baron-Cohen, 2014).

A large body of evidence suggests deficits in implicit mental state attribution to underlie the social interactive impairments observed in ASD (C. D. Frith & Frith, 2012; U. Frith, 2001; Schneider, Slaughter, Bayliss, & Dux, 2013; Senju, 2012). Neuroimaging studies are in support of this claim, demonstrating anatomical and functional abnormalities in the so-called *default mode network*, a brain network relevant for mentalizing processes (Padmanabhan, Lynch, Schaer, & Menon, 2017). However, what are the mechanisms behind this *mindblindness* (Baron-Cohen, 1995)? As has been elaborated in section 1.1, social cognitive abilities might depend on the individual action perception, action experience and action control capacities. Given abnormal movement dynamics as well as abnormal behavioral and neural responses to communicative actions such as interactive gestures or gaze movements (sections 1.3 & 1.4), the implicit access to others' minds via social actions might be compromised in ASD (Cook, 2016; K. L. Marsh et al., 2013). Here, the question arises how social kinematics could be investigated to elucidate the mechanisms behind social impairments. In light of accumulating evidence of distinctive neural signatures of ASD, the study of functional brain dynamics promises the identification of neurobiological *endophenotypes*, i.e. intermediate expressions of a disease between phenotype and genotype (Figure 2). These endophenotypes might not only inform etiological models of ASD or might be predictive of ASD itself, but eventually might offer starting points of clinical interventions (Beauchaine & Constantino, 2017; Maximo, Cadena, & Kana, 2014; Minschew & Keller, 2010). For this purpose, functional magnetic resonance imaging (fMRI) can be used as a method to determine the BOLD brain responses to social actions, thereby indirectly measuring electrical activity of neuronal populations (Logothetis, 2002, for a discussion of fMRI, please see subsection 4.3.1). Considering the above mentioned evidence of ASD-specific functional dynamics, fMRI not only provides valuable insights about functional localization in the brain, but also allows analyzing context-dependent functional integration in terms of functional connectivity between brain regions (Logothetis, 2008).

To summarize, empirical evidence underlines the translational importance of social interactive action signals for social inclusion and mental health in ASD. Thus, in order to extend our understanding of the disease and in order to develop clinical intervention programs that support autistic individuals in dealing with a primarily non-autistic world, we need to investigate the dynamics of social interactions. More specifically, this thesis considered potential mechanisms underlying social cognition, namely the neural expressions of the kinematic access to the minds of others. Therefore, two experimental paradigms in healthy control participants to be used in future clinical patient groups were established to investigate the behavioral and functional BOLD correlates of the brain perceiving and predicting communicative interactions as well as controlling motor responses to social signals.

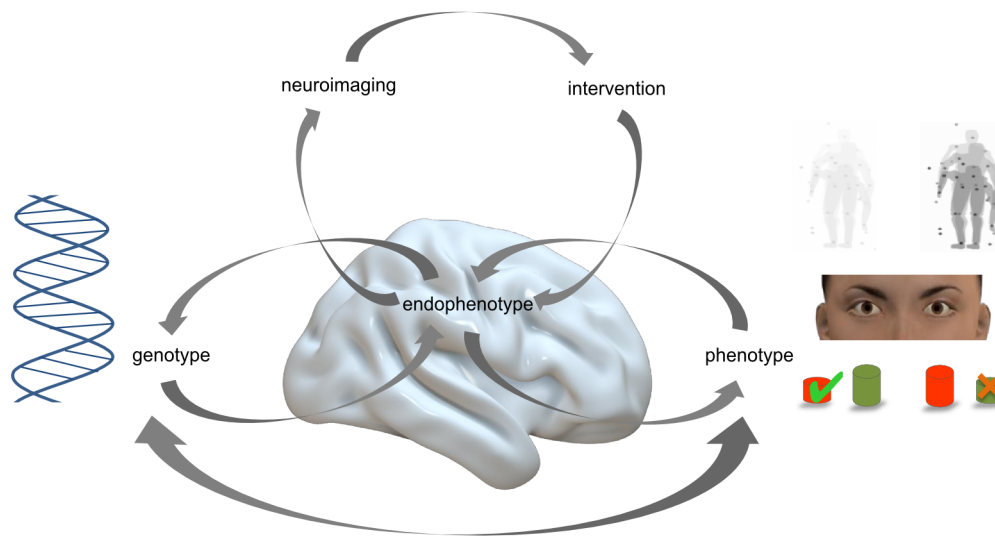


Figure 2. *BOLD correlates as potential endophenotypes in ASD.* Endophenotypes might fill the gap between genetics and phenotypical expression of ASD, for instance atypical perception, gaze behavior, action control, to develop endophenotype-specific interventions that might both have behavioral and epigenetic effects. [Brain image created in Surf Ice (Neuroimaging Informatics Tools and Resources Clearinghouse, retrieved from <https://www.nitrc.org/projects/surface/>); original point-light figure published in Manera, Becchio, Schouten, et al. (2011); virtual character created in Poser 10 (Smith Micro Software, Inc., CA, USA) by L. M. Schliephake]

1.3 Perception & prediction based on communicative actions

1.3.1 From action observation to social cognition

“Social interactions are complex phenomena involving different dimensions of verbal and nonverbal behaviour [...]” (De Jaegher, Di Paolo, & Gallagher, 2010, p. 442). Both verbal and nonverbal communication acts by means of motor processes to produce language or gestures and facial expressions, respectively (Pickering & Garrod, 2013). Underlining the considerable impact of action elements in social interactions, visual motor information about an interaction partner enables spontaneous behavioral synchrony or mimicry (Bailenson & Yee, 2005; Richardson, Marsh, & Schmidt, 2005; Varlet, Marin, Lagarde, & Bardy, 2011). This *chameleon effect* (Kendon, 1970), in turn, has an enhancing effect on attentional and memory processes related to the interaction partner (Macrae, Duffy, Miles, & Lawrence, 2008). Looking through the translational lens, deficits in verbal and nonverbal communication are prominent features of ASD, affecting the execution (Mundy, Sigman, Ungerer, & Sherman, 1986) as well as the perception and neural processing of human locomotion in others (Pavlova, 2012).

Besides behavioral alignment, it has been shown that observed movements, even if the movements of geometric, non-human figures are concerned, are automatically interpreted and motives are attributed to moving agents (Heider & Simmel, 1944). Building on this, accumulating evidence suggests that biological motion actually contains

information about a person's intentions (Becchio et al., 2012). Thus, action observation subserves action understanding, occurring in concert with social metacognition about the thoughts and feelings of another person (Blakemore & Decety, 2001; Rizzolatti & Craighero, 2004). According to the *mirror neuron theory* of the human brain, *action simulation* or *motor resonance* in the motor system of the observing brain, by which one re-experiences the respective action and by which observed actions are integrated onto one's own action portfolio, has been discussed as potential mechanism behind the link between action perception and action understanding (Cook, 2016; Knoblich & Sebanz, 2006; Rizzolatti, Fadiga, Fogassi, & Gallese, 1999; Rizzolatti & Craighero, 2004).

In line with this, brain areas that have been related to mental state attribution, such as the medial prefrontal cortex (mPFC), have been shown activated during the observation of socially meaningful geometric shape movements (Castelli, Happé, Frith, & Frith, 2000). Intellectually non-impaired autistic individuals, however, seem to struggle in attributing intentions to moving shapes, which is associated with reduced cerebral blood flow increases in areas of the mentalizing network and reduced functional connectivity between visual and "social" brain regions (Castelli, Frith, Happé, & Frith, 2002).

1.3.2 Communicative actions and visual perception

In addition to action understanding, it has been demonstrated that the observation of communicative actions enables us to anticipate, i.e. predict, a subsequent complementary action. This effect – known as *interpersonal predictive coding (IPPC)* – (Manera, Becchio, Schouten, et al., 2011; Okruszek, Piejka, Wysokiński, Szczepocka, & Manera, 2017; Sapey-Triomphe et al., 2016) relates to the *Bayesian brain hypothesis* (Adams, Brown, & Friston, 2015; Friston, 2002, 2003), which operationalizes perception as the updated *posterior belief*, i.e. the probability distribution of an internal model of the reality after considering the *likelihood* of the sensory input under the existing internal model predictions (*priors*). Crucially, the posterior belief needs to be updated in order to minimize the prediction error, reflecting the discrepancy between prior predictions and sensory input. Moreover, the precision of prior and likelihood determines the respective impact on the posterior (Figure 3). Specifically, in ambiguous sensory environments that only offer an imprecise likelihood estimation, the weight of prior information increases (Körding & Wolpert, 2004; Todorov & Jordan, 2002). As a consequence, the perception of a scarcely detectable moving agent should be facilitated by a communicative action of another agent that can be used to predict the movement of the hidden agent. While this facilitation effect of IPPC has been demonstrated in healthy subjects (Manera, Becchio, Schouten, et al., 2011), autistic individuals appear not to perceptually profit from communicative as compared to individual, non-predictive actions (von der Lühe et al., 2016). Accounting for this lack of predictive gain by prior information, it is assumed that individuals with ASD fail to integrate internal model predictions or fail to maintain relevant prior information and therefore overemphasize sensory information. This renders them less sensitive to biased perception but at the same time, increases their vulnerability to hyper- or hyposensitivity

(Gómez et al., 2014; Pellicano & Burr, 2012; Top Jr., Luke, Stephenson, & South, 2019). Yet, despite the richness of empirical findings on brain dynamics of predictive coding (e.g. Blank & Davis, 2016; Weilhhammer, Stuke, Hesselmann, Sterzer, & Schmack, 2017), the BOLD correlates of social communicative actions as predictive cues require further attention.

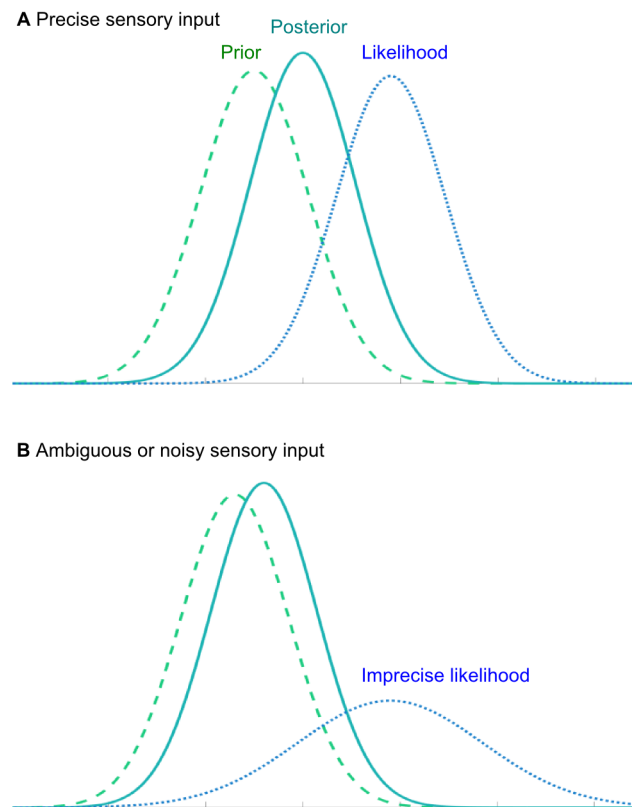


Figure 3. *Impact of sensory uncertainty on Bayesian probabilistic integration.* (A) Precise sensory data (likelihood) considerably influences perception (posterior). (B) In an uncertain sensory environment, prior information is weighted more strongly than imprecise sensory input, dominating perception. [Figure created with Matlab R2017a (The MathWorks, Inc., Natick, MA, USA) and Inkscape 2 (Free Software Foundation, Inc., Boston, MA, USA)]

1.3.3 Investigating IPPC by means of point-light displays

As has been elaborated in the previous section, humans are able to infer biological motion as well as movement intentions from sparse visuo-spatial information (e.g. Becchio et al., 2012; Heider & Simmel, 1944). In order to investigate biological motion perception and the processing of nonverbal cues, researchers have created point-light displays (Figure 4) that constitute of moving dots at anatomically relevant positions, generating the perception of an agent in locomotion (Johansson, 1973). It has been shown that point-light displays reliably convey not only information about the movement direction or the type

of action performed (Pavlova et al., 2017), but also express specific interactive intentions such as behaving cooperatively or rather competitively (Becchio et al., 2012; Manera, Becchio, Cavallo, Sartori, & Castiello, 2011; Manera et al., 2010; Saygin, Wilson, Hagler, Bates, & Sereno, 2004). Moreover, the physical characteristics of point-light stimuli such as the number of light dots, the duration or the speed of dot movements as well as the presence and number of interfering noise dots are highly controllable and can be adjusted to inter-individual differences in visual perception (Manera et al., 2010; Pavlova, 2012).

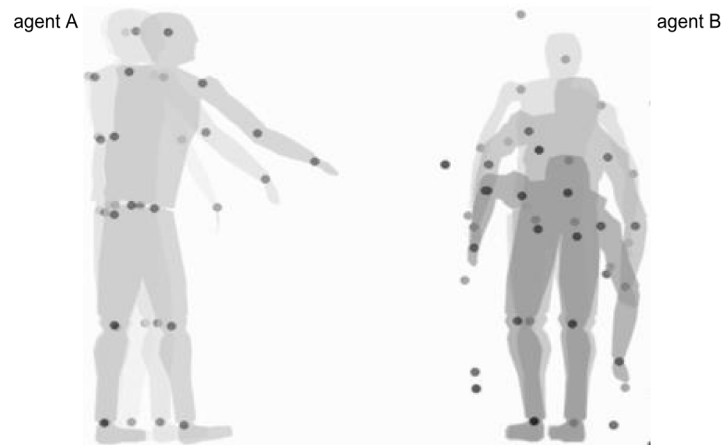


Figure 4. *Point-light displays of two agents.* Moving dots convey the impression of two agents in locomotion. Interfering dots on agent B create a noisy visual display and impede with the perception of the second agent. However, the communicative action (pointing to the floor) performed by agent A predicts a congruent reaction (squats down) of a second agent, facilitating the detection of agent B. Gray silhouettes were invisible for participants. [Original figure published in Manera, Del Giudice, et al. (2011)]

1.3.4 IPPC in a nutshell

Overall, the observation of communicative actions allows us to anticipate a congruent reaction, which might affect our visual perception of a second agent. Yet, the absence of the IPPC effect on reaction time (RT) in individuals with ASD and the lack of knowledge on the BOLD correlates on the phenomenon call for empirical research. The first study of this thesis addressed this empirical gap by means of highly controllable point-light stimuli that reliably convey individual or communicative and, thus, predictive intentions.

1.4 Motor control in a social context & from a second-person perspective

1.4.1 Direct gaze as communicative signal conveying the intentions of another person

In our daily lives, we not only observe social interactions but also actively engage in face-to-face interactions that might have been initiated by direct eye contact (Senju &

Johnson, 2009a). Further stressing the key role of direct gaze as a communicative signal, studies have documented reflexive attentional orientation triggered by direct gaze shifts, an effect that persisted for uninformative and even misleading gaze cues (Driver et al., 1999; Friesen & Kingstone, 1998). Although some evidence suggests that individuals with ASD similarly react to direct gaze and non-social cues (Senju, Tojo, Dairoku, & Hasegawa, 2004), the attentional effect of direct gaze has also been observed in autistic individuals (Fletcher-Watson, Leekam, Findlay, & Stanton, 2008; Swettenham, Condie, Campbell, Milne, & Coleman, 2003). However, diverging from this common ground, ASD has been associated with differential voluntary fixation behaviors towards eyes, leading to the *eye avoidance hypothesis of autism* (Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Moriuchi, Klin, & Jones, 2017; Tanaka & Sung, 2016). Importantly, autistic individuals are thought to lack access to the “mentalistic significance of the eyes” (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997, p. 820): While intellectually non-impaired individuals with ASD do not differ from healthy control participants in deducing the mental state associated with a face, performance significantly decreases when asked to “read the mind” solely from the eye region of another person (Baron-Cohen et al., 1997). Given a negative correlation between task performance in this *Reading the Mind in the Eyes* task and the score in the *Autism Quotient (AQ)* questionnaire (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001), a measure of autistic traits (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001), the insensitivity to the mentalistic content of eyes seems to relate to the spectral position of autistic individuals.

1.4.2 Neural correlates of gaze processing

Neuroimaging studies have consistently found activation in the right temporoparietal junction (TPJ) in response to communicative signals in terms of direct gaze movements (Nummenmaa & Calder, 2009; Senju & Johnson, 2009a). Complementing the gaze-related characteristics of the disorder, atypical BOLD signal as well as functional connectivity of the TPJ in response to direct as compared to averted gaze has been associated with ASD (Pitskel et al., 2011; von dem Hagen & Bright, 2017). Similarly, signal strength and duration of the right TPJ response mirrored the spatial validity of a gaze signal in healthy control participants but not in individuals with ASD, indicating a fundamentally different perception of the meaning, and thus processing, of direct gaze signals in ASD (Pelphrey, Singerman, Allison, & McCarthy, 2003; Pelphrey, Morris, & McCarthy, 2005). For the above reasons and based on the association of meta-analytic brain activation data with the term “gaze” (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011), we defined a subregion of the right TPJ as our region of interest (ROI). Notably, this subregion partly coincides with a posterior functional cluster, relevant in imagination, episodic memory retrieval as well as mentalizing (Bzdok, Laird, Zilles, Fox, & Eickhoff, 2013).

1.4.3 Gaze and action control

Accumulating evidence points towards a modulating effect of the social context on motor actions (Becchio, Bertone, & Castiello, 2008; Becchio, Sartori, Bulgheroni, & Castiello, 2008; Becchio, Sartori, & Castiello, 2010; Wang & Hamilton, 2012). In this sense, studies have revealed that movement dynamics such as velocity, acceleration or deceleration can be influenced by another person's gaze (Castiello, 2003; Hietanen, Nummenmaa, Nyman, Parkkola, & Hämäläinen, 2006; Schilbach et al., 2011). Supporting this claim, it has been shown that direct gaze facilitates motor imitation (Prinsen et al., 2017; Wang, Ramsey, & Hamilton, 2011). Moreover, increased BOLD signal in brain regions such as the inferior frontal gyrus has been indicated to precede the execution of complementary actions (Newman-Norlund, van Schie, van Zuijlen, & Bekkering, 2007), constituting the building blocks of coordinated social interactions (Sartori & Betti, 2015). What is more, given an overlapping neural representation of gazed and grasped at objects, gaze information and motor actions seem to jointly provide access to another person's mind (Becchio, Sartori, et al., 2008; Pierno et al., 2006; Pierno, Becchio, Tubaldi, Turella, & Castiello, 2008). Following on these lines, the inability to automatically integrate gaze information into one's own movement pattern, which has been attributed to ASD (Becchio, Pierno, Mari, Lusher, & Castiello, 2007), might be detrimental to the mentalizing capacities in autistic individuals.

Tightly coupled to motor actions is the inhibition or control of motor reactions. In a social context, we flexibly need to adjust our actions to an interaction partner, thereby modifying our response tendencies in order to perform an action that might be *incongruent* (Nigg, 2000), for example a movement opposite to the direction of a stimulus (Simon, 1969). As has been pointed out earlier, restricted, repetitive behaviors constitute one of the core symptoms in ASD (section 1.2). Meta-analytic evidence further suggests that autistic individuals encounter difficulties in interference control – an effect that was independent on the age of participants but was modulated by intellectual abilities (Geurts, van den Bergh, & Ruzzano, 2014). However, evidence suggests that high-functioning individuals with ASD over-recruit frontal and parietal brain regions involved in response inhibition or response shifting (Schmitz et al., 2006) and that the strength of inhibitory control negatively correlates with the manifestation of autistic traits (Amoruso, Finisguerra, & Urgesi, 2018).

At this point, the question remains how direct gaze influences action control processes. A first study suggests that the lack of direct gaze integration into action control processes persists from low to high action control demands in ASD (Schilbach, Eickhoff, Cieslik, Kuzmanovic, & Vogeley, 2012). Yet, we still lack knowledge about the neural mechanisms behind the interaction of gaze processing and action control (Figure 5) – both in healthy and autistic individuals. Moreover, while researchers have focused on the role of direct gaze as a background stimulus (Böckler, van der Wel, & Welsh, 2014; Wang et al., 2011) or spatial cue (e.g. Engell et al., 2010; Joseph, Fricker, & Keehn, 2015) but not representing the target stimulus, we intended to investigate how direct gaze as compared to averted

gaze interacts with action control if the complementary action resembles a direct reaction to the gaze stimulus itself.

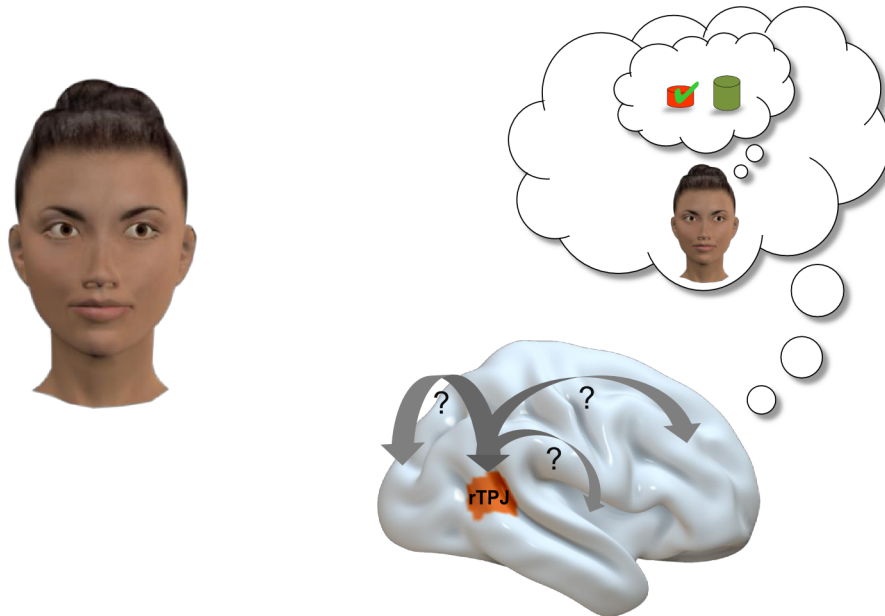


Figure 5. *The role of the right TPJ in integrating gaze information and action control processes.* The right TPJ has been associated with gaze processing and social cognition. Yet, it is unclear how the gaze processing influences action control – particularly under high control demands (left: the virtual character displays a gaze shift to the right of the interaction partner that requires a spatially incompatible button press on the left). [Virtual character created in Poser 10 (Smith Micro Software, Inc., CA, USA) by L. M. Schliephake; brain image created in Surf Ice (Neuroimaging Informatics Tools and Resources Clearinghouse, retrieved from <https://www.nitrc.org/projects/surface/>)]

1.4.4 Face-to-face: third- vs. second-person perspective

Schilbach et al. (2013; 2016; Redcay & Schilbach, 2019) stressed the necessity of studying social interactions from a second-person perspective, i.e. investigating social cognition of interacting instead of observing individuals. While the third-person perspective could enrich our knowledge about social metacognition from a spectators viewpoint, the “second-person experience of other minds” (Schilbach et al., 2013, p. 398) would allow researchers to study social cognition and behavior during active involvement in an interaction. This is of particular importance as studies showed that the brain responses as well as behavioral consequences might differ between observing and experiencing a social interaction (Cavallo, Catmur, Sowden, Ianì, & Becchio, 2014; Holler et al., 2015; Pönkänen, Alhoniemi, Leppänen, & Hietanen, 2011; Schilbach et al., 2006). Furthermore, numerous studies revealed that intellectually non-impaired autistic individuals were able to successfully pass tests that explicitly probe a third-person ToM of an observed person (Bowler, 1992; Peterson, Slaughter, & Paynter, 2007), thereby engaging brain areas similar to those activated in neurotypical control participants (Dufour et al., 2013). The reason for this might be that spectator perspectives might not sufficiently simulate the complexity

of a social interaction and the personal engagement that might involve spontaneous, non-prompted implicit mentalizing that cannot be compensated for by a learned explicit ToM (Senju, Southgate, White, & Frith, 2009). Thus, in order to understand a psychiatric condition such as ASD in the sense of its diagnostic definition as disorder of social interaction and communication, one would need to measure behavior and brain activation in engaged individuals directly experiencing a social interaction (Schilbach, 2016).

1.4.5 Résumé: direct gaze and action control from a second-person perspective

Psychiatric conditions such as ASD co-exist with motor abnormalities such as deficient action control as well as aberrant gaze processing in the TPJ, one of the key brain regions involved in gaze processing. Connecting the two fields, a large body of empirical evidence has revealed a modulating effect of gaze on motor behaviors such as action control of imitated movements. Besides imitation, social interactions also consist of complementary actions that need to be performed as congruent or incongruent reaction to the actions or gaze movements of an interaction partner. Tackling a lack of evidence on the brain mechanisms involved, the second study of this thesis investigated the BOLD correlates and the functional coupling of the TPJ in a context of direct or averted gaze and high or low action control demands. Finally, the usage of a second-person paradigm allowed us to study an experienced interaction with an anthropomorphic virtual character.

1.5 Aims of the thesis

This thesis aimed at investigating the BOLD response to kinematic signals in social interactions. Starting from a third-person perspective to study the predictive nature of social signals and its effects on visual perception, the second study of this thesis adopted a second-person perspective, analyzing the role of the right TPJ in the direct experience of gaze signals and their effects on action control (Figure 6). Pivotaly, by establishing two fMRI paradigms, this thesis aimed at deepening our understanding of the non-pathological brain processes related to action prediction and action control in a socially interactive setting, building the foundation for following translational research on ASD.

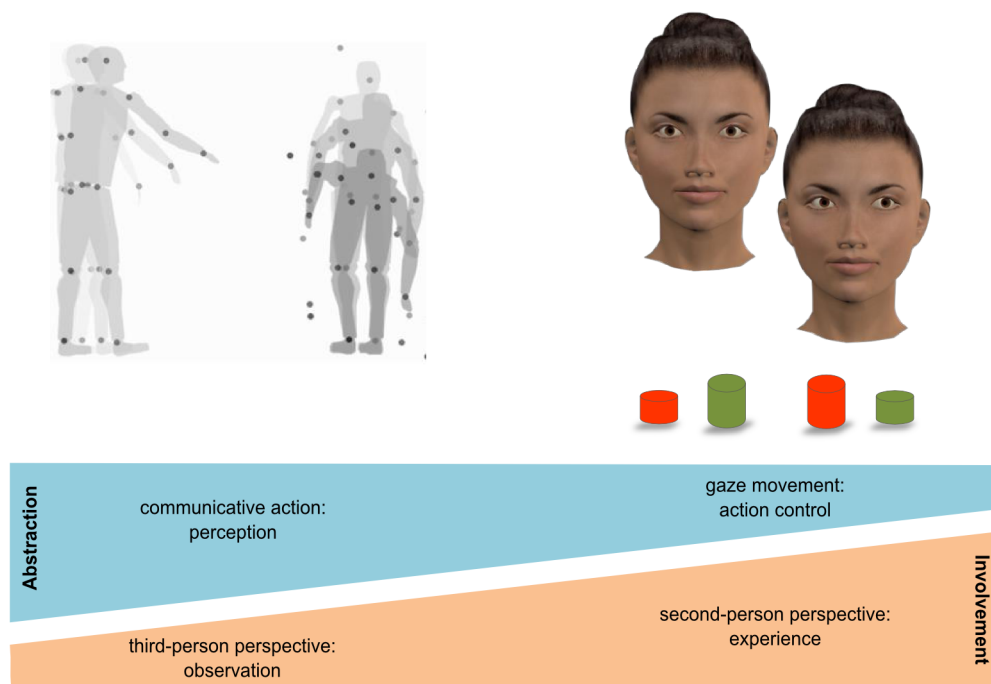


Figure 6. *Conceptual flow of research projects.* While moving from highly abstract action perception in the first study to concrete action execution in study II (blue), participants observe social kinematic interactions from a third-person perspective in the first and experience an interaction with a virtual character from a second-person perspective in the second study (orange). [Point-light agents obtained from the Communicative Interaction Database (Manera et al., 2010; Manera, Del Giudice, et al., 2011); virtual character created in Poser 10 (Smith Micro Software, Inc., CA, USA) by L. M. Schliephake]

2 Perception of Social Kinematics

2.1 Summary


The first study of this thesis (Zillekens, Brandi, et al., 2019) aimed at establishing an experimental paradigm to investigate the behavioral and BOLD correlates of IPPC, which describes the perceptual facilitation effect of communicative as compared to individual actions on visual detection of a second agent (Manera, Becchio, Schouten, et al., 2011; Manera, Schouten, Verfaillie, & Becchio, 2013). To this end, we asked participants to indicate as fast as possible the presence or absence of a second point-light agent B following a communicative or individual action of an initial point-light agent A. The difficulty of the task was controlled for by adjusting the number of interfering noise dots to participants' task performance in a pretest on visual discrimination of point-light stimuli. In a first step, we conducted a behavioral study in 18 healthy participants and replicated findings demonstrating a significantly increased perceptual sensitivity (Manera, Becchio, Schouten, et al., 2011; von der L uhe et al., 2016) and a significantly less conservative response pattern (Manera, Del Giudice, et al., 2011) after communicative as compared to individual actions of agent A. Thus, in line with expectations, IPPC sharpened visual perception and counteracted a non-optimal response strategy. In a second step, we applied the modified paradigm in an fMRI study in 27 healthy participants. Our results showed increased BOLD activation in the right superior frontal gyrus SFG in response to communicative vs. individual actions, corresponding to the SFG's implication in predicting social event sequences (Koechlin, Corrado, Pietrini, & Grafman, 2000; Wood, Knutson, & Grafman, 2004). Contrarily, increased BOLD signal in an *action observation network* was found in the reversed contrast, potentially reflecting a higher demand for executive control (Majerus, P eters, Bouffier, Cowan, & Phillips, 2018; Vossel, Weidner, Driver, Friston, & Fink, 2012) after observing non-predictive, individual actions. Furthermore, over all trials, perceptual discriminability was negatively correlated with the BOLD response in the left amygdala. As a consequence, we analyzed the context-dependent functional connectivity of the amygdala in a psychophysiological interaction analysis, demonstrating increased functional coupling with the mPFC in the context of communicative vs. individual actions and increased functional connectivity with fronto-parietal regions in the context of individual vs. communicative actions. Therefore, the connectivity profile of the amygdala aligned to the experimental context. Fundamentally, an integration of mentalizing computations from the mPFC (Amodio & Frith, 2006; Yang et al., 2015) seems to be specific to a socially predictive environment.

2.2 Contributions and reference

The study “Increased functional coupling of the left amygdala and medial prefrontal cortex during the perception of communicative point-light stimuli” was published in *Social Cognitive and Affective Neuroscience* in 2018. It was conducted under the supervision of ML. B., J.M.L., V.M. and L.S. The research was designed by I.C.Z., A.K., V.M., C.B and L.S. Data analysis was performed by I.C.Z., ML.B, J.M.L. and A.K. All authors critically revised the manuscript written by I.C.Z. C.B. and L.S. provided the funding of the project.

Zillekens, I. C., Brandi, M.-L., Lahnakoski, J. M., Koul, A., Manera, V., Becchio, C., & Schilbach, L. (2019). Increased functional coupling of the left amygdala and medial prefrontal cortex during the perception of communicative point-light stimuli. *Social Cognitive and Affective Neuroscience*, 14(1), 97107. doi: 10.1093/scan/nsy105

Increased functional coupling of the left amygdala and medial prefrontal cortex during the perception of communicative point-light stimuli

Imme C Zillekens,^{1,2} Marie-Luise Brandi,¹ Juha M Lahnakoski,¹ ¹
Atesh Koul,⁴ Valeria Manera,⁵ Cristina Becchio,^{4,6}
and Leonhard Schilbach^{1,2,3}

¹Independent Max Planck Research Group for Social Neuroscience, Max Planck Institute of Psychiatry, 80804 Munich, Germany, ²International Max Planck Research School for Translational Psychiatry, 80804 Munich, Germany, ³Department of Psychiatry, Ludwig-Maximilians-Universität, 80539 Munich, Germany, ⁴Cognition, Motion and Neuroscience Unit, Fondazione Istituto Italiano di Tecnologia, 16152 Genoa, Italy, ⁵CoBTeK Laboratory, Université Cote d'Azur, 06100 Nice, France, and ⁶Department of Psychology, University of Turin, 10124 Turin, Italy

Correspondence should be addressed to Imme C Zillekens, Max Planck Institute of Psychiatry, Kraepelinstr. 2-10, Munich 80804, Germany.
E-mail: imme_zillekens@psych.mpg.de.

Abstract

Interpersonal predictive coding (IPPC) describes the behavioral phenomenon whereby seeing a communicative rather than an individual action helps to discern a masked second agent. As little is known, yet, about the neural correlates of IPPC, we conducted a functional magnetic resonance imaging study in a group of 27 healthy participants using point-light displays of moving agents embedded in distractors. We discovered that seeing communicative compared to individual actions was associated with higher activation of right superior frontal gyrus, whereas the reversed contrast elicited increased neural activation in an action observation network that was activated during all trials. Our findings, therefore, potentially indicate the formation of action predictions and a reduced demand for executive control in response to communicative actions. Further, in a regression analysis, we revealed that increased perceptual sensitivity was associated with a deactivation of the left amygdala during the perceptual task. A consecutive psychophysiological interaction analysis showed increased connectivity of the amygdala with medial prefrontal cortex in the context of communicative compared to individual actions. Thus, whereas increased amygdala signaling might interfere with task-relevant processes, increased co-activation of the amygdala and the medial prefrontal cortex in a communicative context might represent the integration of mentalizing computations.

Key words: interpersonal predictive coding (IPPC); point-light displays; fMRI; action observation network; mentalizing

Introduction

Making sense of non-verbal cues constitutes a key requisite to successfully navigate our everyday social interactions. Non-verbal cues allow us to not only deduce valuable information

about the intentions of another person, but also to anticipate an appropriate response behavior (Becchio *et al.*, 2012; Sapey-Triomphe *et al.*, 2016). Offering excellent experimental control (Pavlova, 2012), point-light displays of human motion have

Received: 31 January 2018; Revised: 2 November 2018; Accepted: 21 November 2018

© The Author(s) 2018. Published by Oxford University Press.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

frequently been used to investigate the perception of non-verbal cues (Neri et al., 2006; Marsh et al., 2009). Numerous studies demonstrated that kinematic information derived from point-light displays can reliably be used to infer the intentions of an actor, consequently facilitating the visual detection of a second agent that responds to a communicative action shown by the first agent (Saygin et al., 2004; Manera et al., 2010, 2011a; Becchio et al., 2012). The underlying phenomenon has been described as interpersonal predictive coding (IPPC; Manera et al., 2013; von der Lühé et al., 2016) and refers to the Bayesian account of the brain as a 'prediction machine' that uses an internal model to generate hypotheses, so-called priors, about the external world (Friston, 2002). While perception relies on a combination of sensory input and priors, the underlying internal models are constantly updated to account for deviating sensory input, namely, the so-called prediction error. Importantly, the Bayesian account assumes that the more ambiguous a sensory environment, the more does the organism rely on prior top-down expectations that drive perception and minimize the prediction error. For instance, a communicative action of an agent might increase perceptual sensitivity in a noisy environment as the sensory input can be compared with a concrete hypothesis about a second agent (prior), facilitating the detection of this second agent (Manera et al., 2011b). Strikingly, the behavioral effect of IPPC of increased sensitivity to discriminate between presence and absence of a second agent was not found in individuals with high-functioning autism, a psychiatric condition that is characterized by impairments in communication and social interaction (von der Lühé et al., 2016).

Despite a growing number of behavioral studies (Manera et al., 2011b; von der Lühé et al., 2016; Okruszek et al., 2017), the neural correlates of IPPC remain elusive. To address this empirical gap, we adapted the paradigm applied by Manera and colleagues (Manera et al., 2011b, 2011c) for neuroimaging purposes. Participants observed point-light agents either performing a communicative or an individual action and were asked to indicate as fast as possible via button press whether a neighboring cloud of dots contained a second agent (Signal) or not (Noise). Our dependent variables were derived from 'signal detection theory' (Stanislaw and Todorov, 1999). We analyzed the sensitivity to discriminate between presence and absence of the second agent, expressed by d' and evaluated the tendency to select one response category (presence) over the other (absence), captured by response criterion c (s. equations 1 and 2). In a behavioral study, we validated the modified paradigm by replicating the enhancing effect of communicative actions on sensitivity d' (cf. Manera et al., 2011b; von der Lühé et al., 2016). Based on previous results Manera, et al., (2011c), we hypothesized participants to be more likely to perceive a second agent after communicative compared to individual actions, which would be expressed by a decreased criterion c in communicative trials. Subsequently, we applied the paradigm in a functional magnetic resonance imaging (fMRI) study to investigate the neural correlates of IPPC. First, to gain a general impression of neural processing during our paradigm, we contrasted activation during task over all experimental conditions against the blood oxygenation level dependent (BOLD) signal in our implicit baseline. Expecting to find regions involved in action observation and biological motion processing such as dorsolateral motor, superior parietal, posterior temporal and visual areas (Caspers et al., 2010; Pavlova, 2012), we next analyzed the specific effects of communicative and individual actions on neural signaling. Representing socially interactive and hence, predictive stimuli, we anticipated communicative contrary to individual actions to evoke an increased

BOLD response in core areas of the so-called 'social brain' such as medial prefrontal and orbitofrontal cortex, which have been linked to the attribution of intentions, dynamic social perception (Amodio and Frith, 2006; Yang et al., 2015) as well as the processing of frequent and predictable event sequences (Wood et al., 2004). We additionally evaluated the BOLD response to non-predictive, individual actions and the interaction of experimental conditions by contrasting non-expected trial outcomes (Noise after communicative actions and Signal after individual actions) to expected trial outcomes (Signal after communicative actions and Noise after individual actions). Moreover, we were interested in the brain correlates of the two 'signal detection theory' parameters d' and c . Although van Kemenade et al. (2012) measured a reduction in sensitivity to biological motion and a shift in response criterion toward positive responses after repetitive transcranial magnetic current stimulation over the premotor cortex, the neural correlates of perceptual discriminability and response tendencies rest largely unknown, particularly in a paradigm of predictive and non-predictive action cues potentially recruiting higher-order neural computations (van Pelt et al., 2016). Thus, in our study, we correlated the participants' sensitivity d' and criterion c values with neural activation during the task compared to baseline. Observing that neural activity in the amygdala was negatively associated with d' , we consequently conducted a psychophysiological interaction analysis to further assess how the connectivity of the amygdala is modulated by the communicative as compared to the individual context.

Methods

Participants

Of the 21 healthy volunteers in the behavioral validation study, 2 participants were excluded from the analysis as their performance did not significantly exceed chance level (Mueller-Putz et al., 2008). Responses of another participant could not be recorded. Of the remaining 18 participants, 9 were female. The age ranged between 20 and 29 years ($M = 23.22$, $s.d. = 2.76$). In the fMRI study, caused by the temporal constraints and difficulty of the paradigm, which had the purpose of triggering false positive (FA) responses, 9 out of 50 participants did not achieve a performance above chance level. Due to missing data, two data sets were lost. Furthermore, nine participants did not fulfill the requirements of the fMRI analysis (≥ 16 valid trials in each combination of condition). We additionally excluded two participants who showed repeated translational motion (> 3 mm) as well as neural signal loss due to susceptibility artifacts. In one participant, an anatomical screening procedure revealed abnormalities. Thus, the final sample of the fMRI study comprised 13 female and 14 male participants, aged 20–50 years ($M = 26.63$, $s.d. = 6.55$). All participants of both the behavioral and the fMRI study were right-handed (Oldfield, 1971), had normal or corrected to normal vision and no history of neurologic or psychiatric illness. Independent of the performance in the task, participants received a monetary compensation of 10€ per hour. The experimental procedures followed the guidelines of the Declaration of Helsinki and were approved by the ethics committee of the Ludwig-Maximilians-Universität München.

Experimental design

In the present study, we used an adapted version of a previously published yes-no paradigm (Manera et al., 2011c). Using Psychophysics Toolbox (Version 3.0.11.: Brainard, 1997;

Table 1. Experimental conditions. Actions of agent A define communicative (COM) and individual (IND) trials, whereas the presence or absence of agent B defines trials as Signal or Noise trials, respectively. Given the combination of a communicative action of agent A and the presence of agent B (COM and Signal), agent B's response action corresponds to the communicative action of agent A.

Communicative (COM)	Agent A	Individual (IND)	Signal	Agent B	Noise
Asking to squat down		Turning around	Squatting down		Absent
Asking to look at the ceiling		Sneezing	Looking at the ceiling		Absent
Asking to sit down		Drinking	Sitting down		Absent

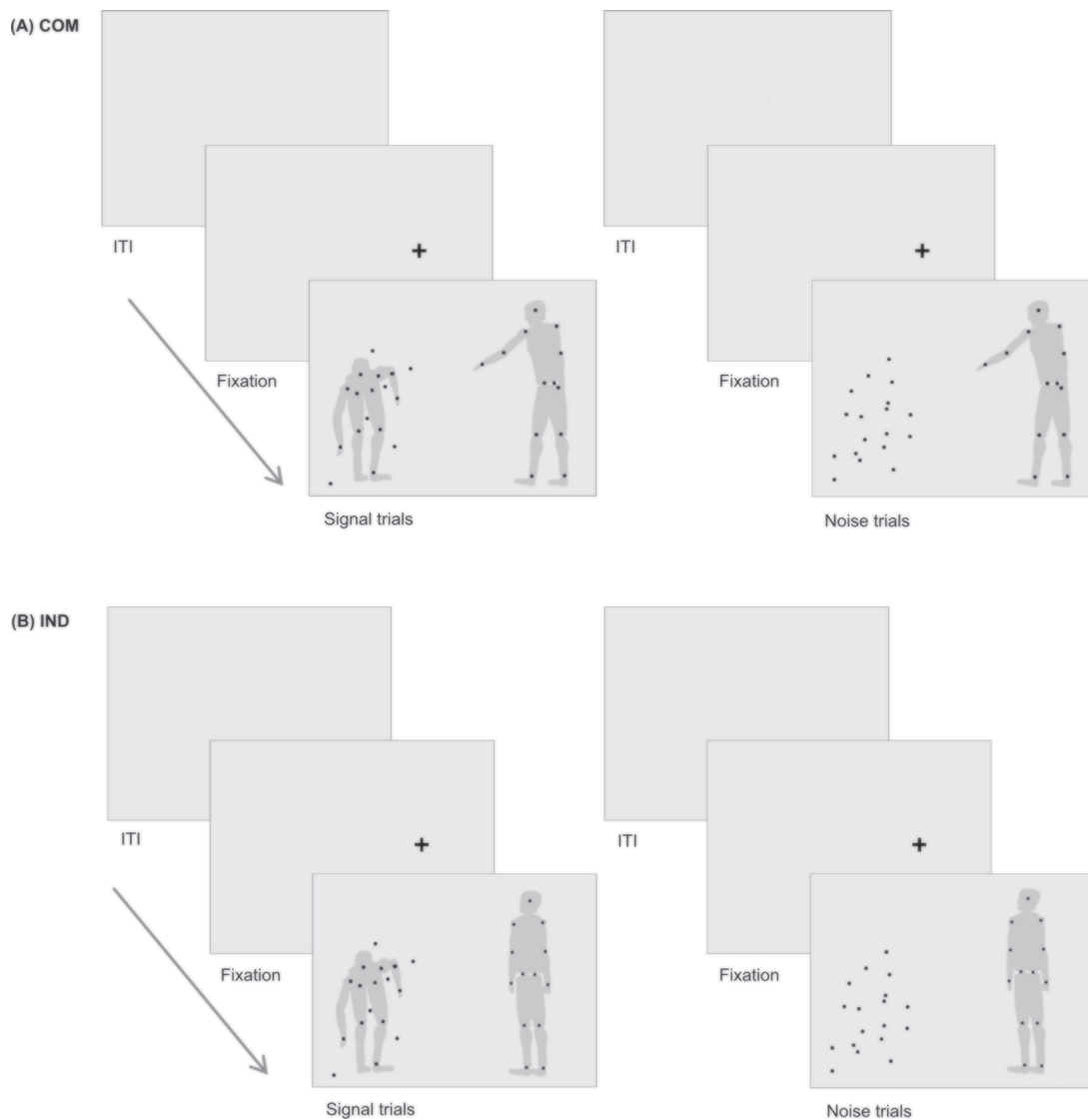


Fig. 1. Structure of experimental trials. Jittered ITIs preceded a fixation cross appearing at the subsequent position of agent A. Participants were asked to first, look at agent A, second, fixate the cloud of dots and third, indicate the presence (Signal) or absence (Noise) of agent B via a button press. (A) depicts trials of the communicative condition (COM); (B) exemplifies the individual condition (IND). On the left, agent B is present (Signal trial), reacting in accordance to the communicative action of agent A. On the right, agent B is replaced by randomly moving noise dots (Noise trial). The gray silhouettes serve illustrative purposes and were not visible for participants.

Kleiner et al., 2007) in Matlab R2015a (The MathWorks, Inc., Natick, Massachusetts, USA), we presented black moving dots on a gray background. On one side of the computer monitor (refresh rate = 59 Hz, resolution of 1024×768 , viewable region of 375×280 mm), moving dots constituted an agent (agent A), who performed a communicative (COM) or an individual (IND) action (Table 1). On the other side of the screen, a cloud of

temporally and spatially scrambled moving dots was displayed (for details, see Manera et al., 2011c). In 50% of trials, a second agent (agent B) was present within the cloud and reacted to the action of agent A (Signal trials); in the remaining 50% of trials, the dots' motion was scrambled (Noise trials; Figure 1). From this 2 (type of action) $\times 2$ (type of trial) design we obtained four experimental conditions: COM_Signal, COM_Noise, IND_Signal

and IND_Noise. Although being presented simultaneously, agent B's action always succeeded agent A's action without any temporal delay. Movements of the agents were chosen from the Communicative Interaction Database and have been shown to be reliably recognizable (Manera et al., 2010, 2011c). Stimulus duration ranged from 2885 to 3473 ms and the distance from the center of the screen was comparable between actions. To avoid participants' reliance on simultaneous transitions of dots defining agent B's body, we applied a so-called limited lifetime technique (Burr et al., 1998; Neri et al., 2006). Of 13 possible positions constituting agent B, only 6 were occupied by Signal dots at a given time. The 'lifetime' of the dots was limited because after 200 ms, a dot disappeared and reappeared at another position. Desynchronized timing of dot appearance further prevented joint transitions of stimuli. The position of agents on the left or right side of the screen was counterbalanced.

Procedure

Participants either took part in the behavioral or the fMRI study. After providing written informed consent, they completed a pretest and the main part of the experiment. The pretest consisted of 108 trials and served at defining the individual level of noise dots to be employed. For this purpose, we presented the cloud of dots potentially containing agent B, and manipulated the difficulty in the task of correctly indicating the presence or absence of agent B by employing a cloud of 5, 20 or 40 dots. Fitting a cumulative Gaussian function to participants' performance, we derived the number of dots corresponding to a performance of 70% correct responses. Pursuing Manera et al.'s (2011a, 2011b) procedure, if the estimated number of dots was lower than five, it was set to five. The participant-specific number of noise dots estimated with this procedure was utilized in the main part of the experiment, which consisted of 144 trials in the behavioral study and of 192 trials in the fMRI study. During four example trials, the participant was familiarized with the task. Each trial was preceded by a fixation cross indicating the subsequent position of agent A and followed by a blank screen for a jittered inter-trial-interval (ITI) with mean duration of 2 s (range = 1–3 s) in the behavioral and 4 s (range = 3–5 s) in the fMRI study. The participant was instructed to initially fixate agent A, then look at the cloud of dots and indicate as soon as possible whether agent B was 'present' or 'absent'. Responses could be given as long as stimuli were presented. Across participants, the position of the response buttons [s- or l-key on a standard German (QWERTZ) keyboard or left or right button on a button box in the main part of the fMRI study] was counterbalanced. While completing the task, an eye-tracking camera (EyeLink 1000 Plus; SR Research, Osgoode, ON, Canada) recorded participants' right eye with a sampling rate of 1000 Hz. In the fMRI study, an MRI-compatible version of the same eye-tracking system was used. After a 9-point calibration and validation procedure, the fixation duration on agent A was evaluated online and participants would be shown a warning message if the fixation was shorter than 1000 ms in 3 consecutive trials, sensitizing participants to initially fixate agent A.

Behavioral data analysis

Behavioral data analysis was performed in Matlab R2015a. Effect sizes (Cohen's d_z) cited in this paper represent statistics described in Lakens (2013). For the pre-processing of eye-tracking data, we used the software package edar by Tore Erdmann

(<https://github.com/toreerdmann/edar>; retrieved 26 July 2017) in R (Version 3.3.1, R Foundation, Vienna, Austria).

Fixation durations represented the cumulative duration of all initial fixations over all trials, i.e. static eye positions longer than 100 ms (Version 1.5.0, EyeLink 1000 User Manual) with time points of blinks being removed from the data. If participants fixated each agent for 200 ms or more, i.e. spend at least 200 ms on the side of the screen on which the respective agent or Noise was presented, a trial was declared as 'valid'. We further excluded trials in which a response was given after the stimuli had already disappeared or before fixating agent B (s. Supplementary Table S1 for details). Reaction times (RTs) comprised the time window between the last fixation on agent A and a button press. All subsequent analyses were based on valid trials.

In order to obtain the two 'signal detection theory' parameters sensitivity d' and response criterion c , we calculated the FA rate (proportion of false positive responses of all Noise trials) and hit rate (proportion of true positive responses of all Signal trials). Next, hit and FA rates were z-transformed and employed through the following formulas:

$$d' = Z(\text{Hit rate}) - Z(\text{FA rate}) \quad (1)$$

$$c = -(1/2) * [Z(\text{Hit rate}) + Z(\text{FA rate})] \quad (2)$$

Testing the assumption that IPPC increases perceptual sensitivity, we compared d' in the communicative to the individual condition by employing paired one-sided t-tests. Using the same statistical analyses, we addressed our expectation of a bias toward responding 'present', i.e. a lower criterion in communicative compared to individual trials. Last, to exclude an association of length of evidence accumulation and perceptual sensitivity, we correlated the fixation duration on agent B/Noise with d' .

fMRI acquisition and data analysis

In the fMRI study, the main part of the experiment took place inside a 3T MR scanner (MR750; GE, Milwaukee, USA). For design efficiency reasons (Henson, 2007), we added 35 null trials of 4 s duration to the design prolonging the ITI and representing our baseline trials. The experiment comprised a single functional run of 791 volumes of 40 slices (32-channel head coil, AC-PC-orientation, 96×96 matrix, 3×3 mm voxel size, 3 mm slice thickness, 0.5 mm slice gap, echo planar imaging [repetition time (TR) of 2000 ms, echo time (TE) of 20 ms, 90° flip angle]). By removing the first nine volumes, we controlled for T1 non-equilibrium effects. fMRI data pre-processing and analysis were performed in SPM12 (Statistical Parametric Mapping Software, Wellcome Department of Imaging Neuroscience, London, UK, <http://www.fil.ion.ucl.ac.uk/SPM>). By the means of rigid body transformation, functional images were spatially realigned to the mean image. After coregistration, images were spatially normalized to the Montreal Neurological Institute (MNI) template using tissue segmented T1-weighted anatomical images (BRAVO FSPGR pulse sequence, 1 mm isotropic voxels, TR of 6.2 ms, TE of 2.3 ms). Voxels of functional images were resliced to $2 \times 2 \times 2$ mm. For spatial smoothing, we applied a 3D Gaussian Kernel with full width of half maximum of 8 mm. Experimental trials as well as baseline trials were modeled as single epochs of trial duration in a general linear model (GLM) and convolved with a hemodynamic response function. Four regressors accounted for the experimental conditions of trial type (Noise vs Signal trial) x type of action [communicative (COM) vs individual (IND)]. No

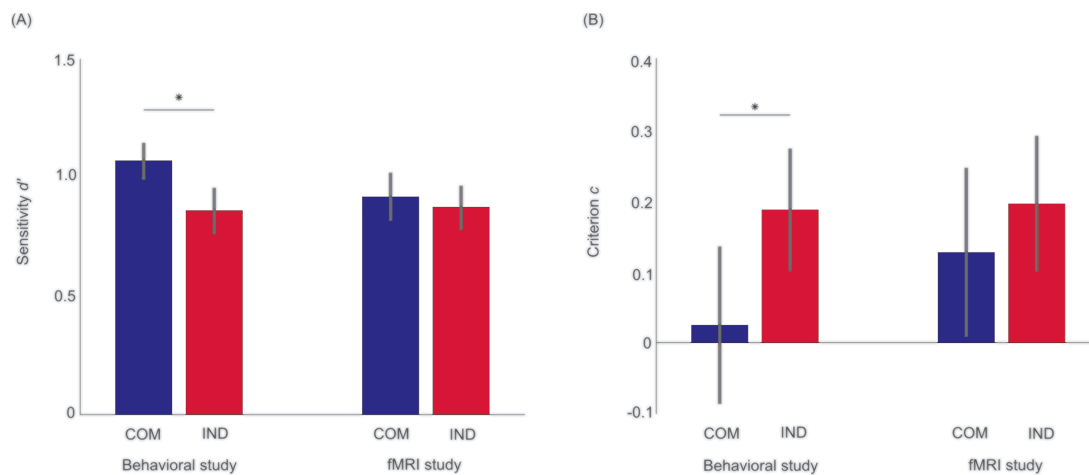


Fig. 2. Effect of IPPC on signal detection theory parameters. (A) Mean sensitivity d' values and (B) mean criterion c values in the communicative (COM) and individual (IND) conditions of the behavioral and the fMRI study. Error bars represent the standard error of the mean (SEM), the asterisks mark statistically significant ($P < 0.05$) differences.

global scaling was applied and low-frequency signal drifts were filtered using a cut-off period of 128 s. Voxel-wise maximum likelihood estimators were estimated thereby considering the temporal autocorrelation of the data (Kiebel and Holmes, 2004). On the first level, we included six motion regressors and two regressors capturing the first principal component of confounding signal from white matter (WM) and cerebrospinal fluid (CSF), which on average accounted for 86% (s.d. = 3%) and 79% (s.d. = 5%) of the variance in the signal from WM and CSF, respectively (Caballero-Gaudes and Reynolds, 2017). For this, we obtained a binarized mask from the respective structural images using a 0.95 threshold in SPM's image calculator (imcalc) and performed a principal component analysis of signals in WM and CSF for each participant. Finally, invalid trials were captured by a regressor of no interest. On the second level, a flexible factorial design was set up, analyzing condition effects on the group BOLD contrast. A subject factor was added to the design and SPM12's default settings of unequal variances over experimental conditions and subjects were implemented. We analyzed the main effect of communicative actions [(COM_Signal + COM_Noise) > (IND_Signal + IND_Noise)] and the reversed contrast of individual actions [(IND_Signal + IND_Noise) > (COM_Signal + COM_Noise)], as well as the main effects of presence [(COM_Signal + IND_Signal) > (COM_Noise + IND_Noise)] and absence of agent B [(COM_Noise + IND_Noise) > (COM_Signal + IND_Signal)]. Calculating experimental interactions of experimental main effects, we included a contrast of expected outcome (EO) [(COM_Signal + IND_Noise) > (IND_Signal + COM_Noise)], i.e. trials including agent B reacting to a communicative action and Noise following individual actions of agent A subtracted by activation during Noise after communicative and Signal after individual actions. Similarly, we calculated the reversed contrast of non-expected outcome (NEO) [(COM_Noise + IND_Signal) > (COM_Signal + IND_Noise)]. Additionally, on the second level, we performed a regression analysis defining sensitivity d' over both conditions as a covariate of interest in a one-sample t -test of task compared to baseline activation and repeated the procedure for criterion c as a covariate of interest. Finally, we explored if and how the functional coupling of the amygdala as a region of negative association with perceptual sensitivity differs between communicative and individual actions. To this end, we

conducted a generalized condition-specific psychophysiological interaction analysis (McLaren et al., 2012). ROI (region of interest) coordinates were derived from Neurosynth [Yarkoni et al., 2011; (-22 -4 -18); term = 'Amygdala'; zscore = 33.11; retrieved 12 September 2017, from www.neurosynth.org] and ROI spheres of 6 mm radius were created with marsbar toolbox (Brett et al., 2002). We extracted the eigenvariate and allowed actual ROIs to vary in size between participants ('equalroi' = 0) but restricted them to first-level masks generated by SPM12 to find brain correlates in the context of communicative compared to individual actions and vice versa. Statistical maps are shown at a cluster forming threshold of $P < 0.005$ (uncorrected) and a cluster threshold of $P < 0.05$ (FWE). Maps of the psychophysiological interaction analysis are presented at a threshold of $P < 0.05$ (FWE) at voxel level and a cluster size of $k > 100$, considering the smoothness of the data. For functional localization we utilized the Anatomy Toolbox (Eickhoff et al., 2005) (Version 2.2c) and applied Surf Ice from (<https://www.nitrc.org/projects/surface/>) and MRICron (Rorden and Brett, 2000) for all brain visualizations.

Results

Behavioral results

The average difficulty in the behavioral experiment was 10.56 (s.d. = 6.20) interfering dots. As intended, participants correctly identified Signal or Noise in 70.53% (s.d. = 6.80%) of valid trials. In comparison, implementing a mean number of 12.19 dots (s.d. = 8.36) in the fMRI experiment, participants achieved a performance of 69% (s.d. = 7.6%) correct responses. Confirming our hypothesis, a paired one-sided t -test attested a significant increase of d' in communicative ($M = 1.34$, s.d. = 0.39) compared to individual trials ($M = 1.08$, s.d. = 0.53) in the behavioral study, $t(17) = 2.30$, $P < 0.05$, $d_z = 0.56$. In the fMRI study, the effect of sensitivity being higher in the communicative ($M = 1.15$, s.d. = 0.61) compared to the individual condition ($M = 1.10$, s.d. = 0.59) remained non-significant, $t(26) = 0.64$, $P = 0.26$ (Figure 2A). Concerning the impact of the type of action on participants' response bias, in the behavioral study, participants were more biased toward reporting the presence of a second agent in communicative ($M = 0.02$, s.d. = 0.47) than in individual

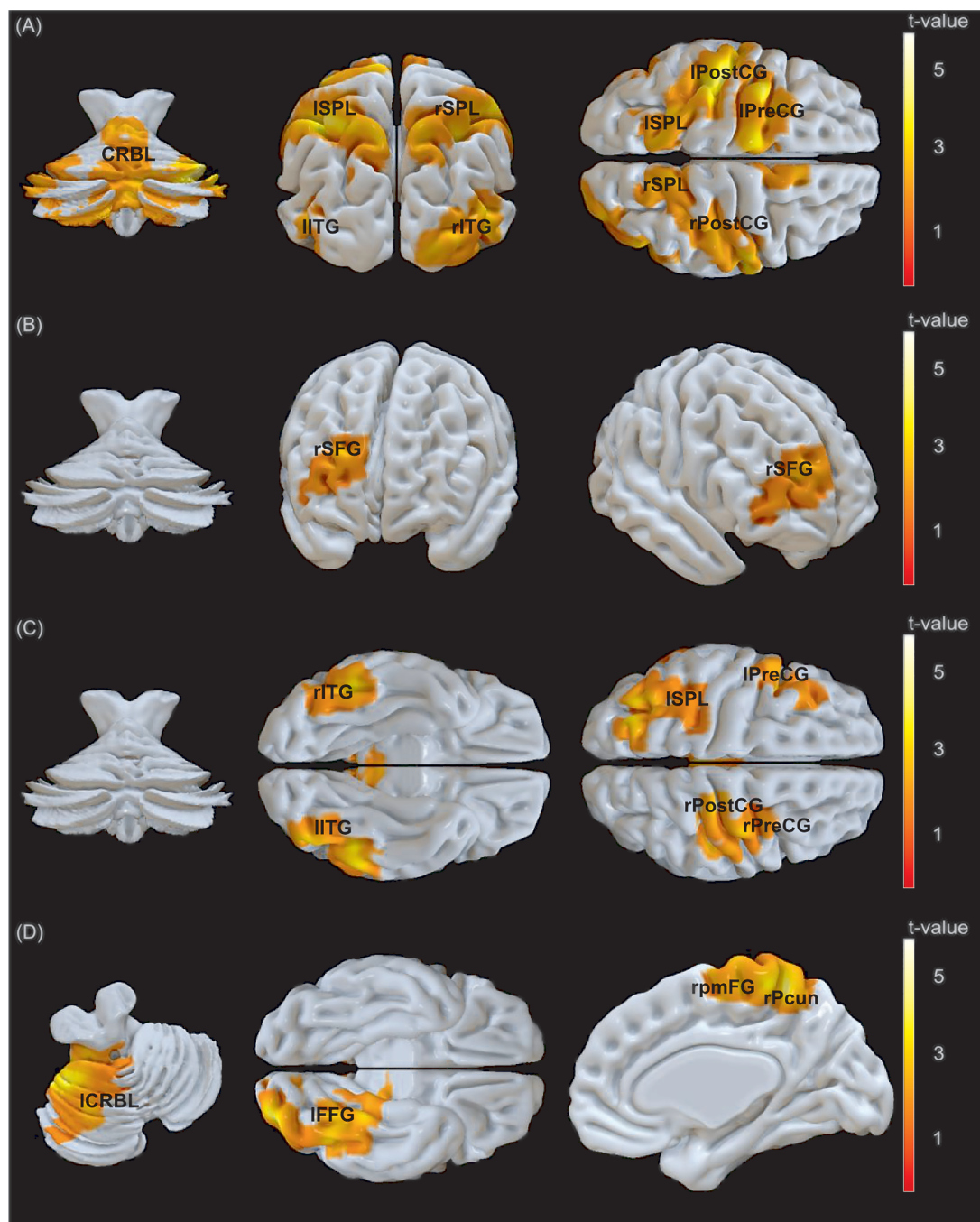


Fig. 3. (A) Clusters of activation of the contrast task greater than baseline, the main contrasts of (B) communicative vs individual (COM > IND), (C) individual vs communicative (IND > COM) trials and (D) the interaction effect of conditions, depicting the contrast of NEO vs EO. The cluster forming threshold was set to $P < 0.005$ (uncorrected), the cluster threshold to $P < 0.05$ (FWE) and cluster size (A) $k > 1026$ voxels, (B) $k > 507$ voxels, (C) $k > 1078$ voxels and (D) $k > 565$ voxels. [(A) CRBL, cerebellum; l/rSPL, left/right superior parietal lobule; l/rITG, left/right inferior temporal gyrus; l/rPostCG, left/right postcentral gyrus; l/PreCG, left precentral gyrus; (B) rSFG, right superior frontal gyrus; (C) l/rITG, left/right inferior temporal gyrus; ISPL, left superior parietal lobule; rPostCG, right post-central gyrus; l/rPreCG, left/right pre-central gyrus; (D) ICRBL, left cerebellum; IFFG, left fusiform gyrus; rpmFG, right posterior medial frontal gyrus; rPcun, right precuneus]

trials ($M = 0.19$, $s.d. = 0.50$), $t(17) = 2.61$, $P < 0.01$, $d_z = 0.63$. Similarly, in the fMRI study, a paired one-sided t -test revealed a trend of c being lower in the communicative condition ($M = 0.13$, $s.d. = 0.44$) than for individual actions ($M = 0.20$, $s.d. = 0.49$), $t(26) = 1.20$, $P = 0.12$ (Figure 2B).

Crucially, d' and c were uncorrelated in both studies and could thus be used as independent predictors in our brain-behavior correlation analysis [behavioral: $r(16) = -0.10$, $P = 0.69$; fMRI: $r(25) = 0.16$, $P = 0.44$]. Furthermore, a null correlation between the fixation duration on agent B/Noise and d' in the behavioral

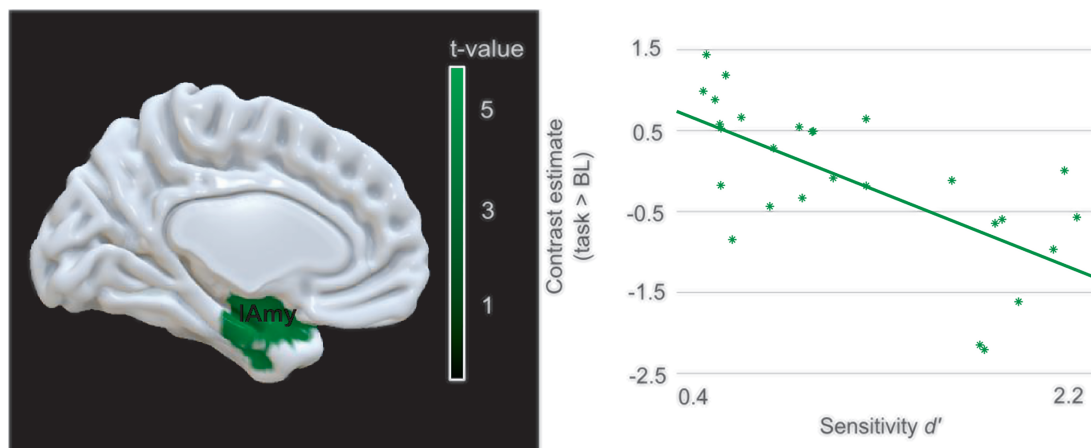


Fig. 4. Task-related brain activity modulated by participants' sensitivity d' . Brain activity map depicting brain regions whose neural activation during task compared to baseline negatively correlated with sensitivity d' . The scatterplot visualizes the relationship of sensitivity d' with the contrast estimates of the respective peak region. The cluster forming threshold was set to $P < 0.005$ (uncorrected), the cluster threshold to $P < 0.05$ (FWE) and cluster size $k > 260$ voxels. [lAmy, left amygdala]

study ruled out that prolonged fixation of the cloud determined participants sensitivity d' , $r(16) = -0.03$, $P = 0.90$. Equally, in the fMRI study, fixation duration and sensitivity were uncorrelated $r(25) = 0.12$, $P = 0.55$ (s. [Supplementary Tables S2 and S3](#) for details).

Supplemental paired one-sided t -tests were used to investigate condition-specific differences in the sub-components of d' and c , namely the FA and true positive (hit) rates. To correct for multiple comparisons, we Bonferroni corrected the original alpha level of 0.05 for the two independent tests for each sub-component. Results show that the FA rate did not differ between conditions neither in the behavioral [$t(17) = 0.27$, $P = 0.39$] nor the fMRI study [$t(26) = 0.93$, $P = 0.18$]. The hit rate, however, was significantly larger in communicative compared to individual trials in the behavioral study, $t(17) = 2.87$, $P < 0.01$. This pattern emerged as a trend in the fMRI study, $t(26) = 1.68$, $P = 0.053$.

Neural correlates

Task compared to baseline elicited bilateral neural activation in the inferior and superior parietal lobules, post- and the left pre-central gyri, inferior temporal, occipital and cerebellar regions ([Figure 3A](#) and [Supplementary Table S4](#)). The first main contrast, namely communicative contrasted to individual trials [(COM_Signal + COM_Noise) > (IND_Signal + IND_Noise)], was associated with significantly higher BOLD signal in the right superior frontal gyrus (SFG) ([Figure 3B](#)), an effect primarily driven by the contrast of COM_Noise > IND_Signal ([Supplementary Figure S1](#)). The reversed contrast [(IND_Signal + IND_Noise) > (COM_Signal + COM_Noise)] was accompanied by an increased BOLD response in the left superior parietal lobule, inferior temporal gyri as well as frontal areas with peaks in the pre-central and the right post-central gyri ([Figure 3C](#)). Depicting the interaction effects of experimental conditions, the EO contrast [(COM_Signal + IND_Noise) > (IND_Signal + COM_Noise)] did not evoke any suprathreshold activation, whereas the reversed NEO contrast [(COM_Noise + IND_Signal) > (COM_Signal + IND_Noise)] showed activation in the right posterior medial frontal gyrus (PMFG), bilateral precune, left cerebellum and left fusiform gyrus (FFG; s. [Figure 3D](#); [Supplementary Tables S5 and S6](#) for all main and interaction effects of experimental conditions).

Brain-behavior correlations

To shed light on the relationship of neural activation and the 'signal detection theory' parameters across subjects and across conditions, sensitivity d' and criterion c values were used as covariates of interest in two separate second-level analyses of activation differences for task compared to baseline. While we did not find a positive correlation, the first analysis showed a negative association of sensitivity d' and activity in a left lateralized cluster in the inferior temporal gyrus including peak activation in the amygdala. In the second regression analysis, we neither identified a significant positive nor negative neural correlate of subject-specific criterion values ([Figure 4](#) and [Supplementary Table S7](#)).

Connectivity analysis

A psychophysiological interaction analysis was used to investigate the functional coupling of the left amygdala in the context of communicative and individual actions ([Figure 5](#) and [Supplementary Table S8](#)). For individual contrasted to communicative actions (IND_Signal + IND_Noise) > (COM_Signal + COM_Noise), the left amygdala co-activated with a dorsal fronto-parietal network comprising bilateral inferior and superior parietal lobules and the middle frontal gyri, spreading to the pre-central gyri and the left inferior frontal gyrus. Additionally, co-activation was spread over the inferior temporal gyri and cerebellum. In response to communicative compared to individual actions [(COM_Signal + COM_Noise) > (IND_Signal + IND_Noise)], activation in the amygdala was coupled to activation in a prominent bilateral cluster in medial prefrontal cortex (mPFC) consisting of superior medial and orbitofrontal gyri and the right anterior cingulate cortex. Peak co-activation also occurred in the left temporal pole (Tp).

Discussion

In the present study, we used an fMRI-compatible version of an established signal detection task to investigate the behavioral and neural correlates of IPPC. We replicated the behavioral finding of higher sensitivity and less conservative response criteria in communicative compared to individual actions and demonstrated that this effect was driven by a higher proba-

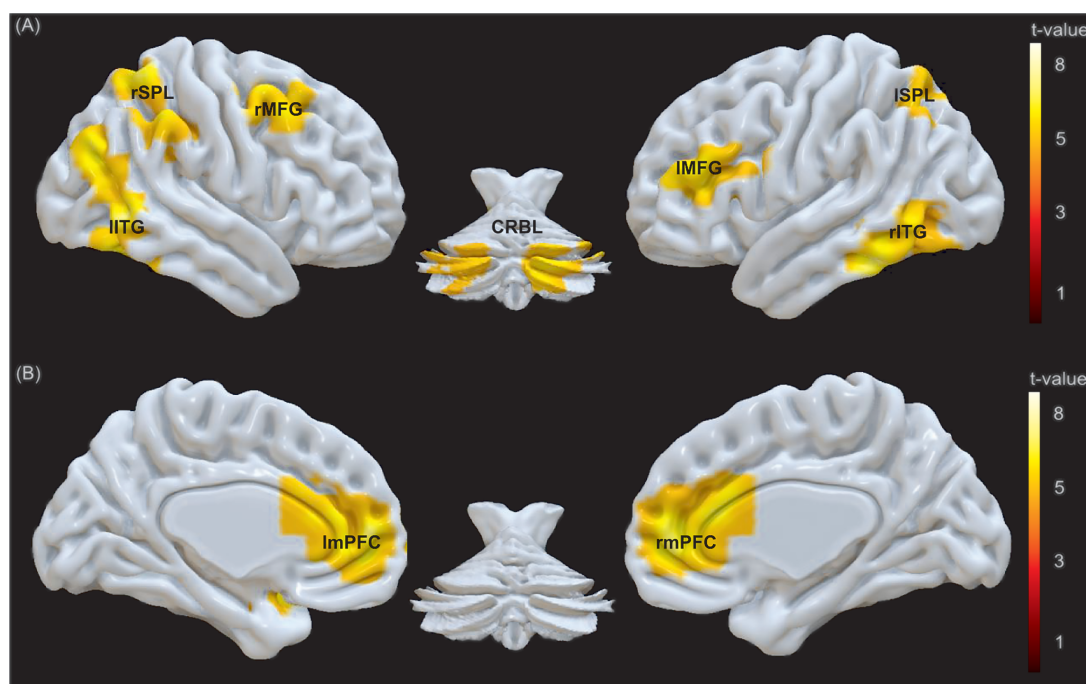


Fig. 5. Modulation of connectivity of the amygdala by action type. Co-activation of the amygdala as seed region for the contrasts (A) individual vs communicative (IND > COM) and (B) communicative vs individual (COM > IND). The threshold was set to $P < 0.05$ (FWE) at voxel level and cluster size $k > 100$. [(A) l/rITG, left/right inferior temporal gyrus; l/rSPL, left/right superior parietal lobule; l/rMFG, left/right middle frontal gyrus; CRBL, cerebellum; (B) l/rmpPFC, left/right medial prefrontal cortex including peak voxels in the superior medial and orbitofrontal gyri as well as in the anterior cingulate cortex]

bility to correctly detect a second agent but was not reflected in an increased rate of FA responses. On the neural level, the right SFG was shown to be sensitive to communicative action cues, specifically, if predictions drawn from them were violated. Furthermore, neural activation in the amygdala was negatively correlated with perceptual sensitivity. Building on this, in a subsequent psychophysiological interaction analysis, we identified two distinct modes of operation. In the context of individual actions, the amygdala increased its functional connectivity with fronto-parietal areas, whereas in a context of communicative signals, the amygdala was functionally coupled to the mPFC.

While replicating the effects of IPPC on sensitivity d' and response criterion c , namely higher d' values and less conservative response criteria after communicative compared to individual actions in the behavioral study, effects commuted to non-significant trends in the fMRI study. Despite carefully controlling task difficulty and gaze behavior of participants as had been done in the behavioral study, it needs to be considered that the pre-test was performed outside of the scanner. Therefore, participants had to cope with a change in environment when performing the main part of the experiment inside the MRI scanner.

In line with our expectations, for the main effect of task vs baseline, we found bilateral neural activation in frontal motor areas, superior parietal, inferior temporal and visual areas, constituting an action observation network (Caspers et al., 2010) and representing key regions for biological motion perception (Pavlova, 2012). Diverging from this activation map, perception of communicative actions, particularly if this communicative action is not followed by a congruently reacting agent B but Noise, led to a differential increase of neural activity in a laterally spread right SFG, a region that has been attributed to prospective memory and future planning (Barbey et al., 2009;

Underwood et al., 2015). By incorporating predictions drawn from episodic event knowledge (Bludau et al., 2014) the SFG is assumed to be particularly sensitive to the violation of predictions (Wood et al., 2004). Accordingly, we find the strongest SFG activation in response to communicative actions that are not followed by an expected second agent. Contrary to our expectations, communicative actions compared to individual actions did not lead to an increased BOLD signal in the mPFC. An explanation for this might be that although only communicative actions represented signals of social consequences, a point-light agent always represented a social entity. Moreover, repeated presentation of communicative stimuli might have suppressed the neural response in the mPFC (Heleven and Van Overwalle, 2016). Eventually, it needs to be considered that the present task might not evoke any changes in mPFC activation. In comparison, by recruiting inferior temporal, superior parietal and frontal regions, individual compared to communicative actions activated a neural network similar to the task vs baseline contrast. Besides forming part of an action observation network and thus, realizing biological motion or action processing (Caspers et al., 2010; Pavlova, 2012), dorsal fronto-parietal areas are thought to execute top-down attentional control in order to cope with high demands during early visuo-perceptual processing (Majerus et al., 2018; Vossel et al., 2012). In concordance with this, participants adopted a conservative response strategy when being confronted with individual actions, reporting the presence of a second agent less often than after communicative actions.

Second, we investigated the interaction effects of conditions on neural activation. In accordance with the predictive coding account (Friston, 2002) and empirical findings that assume the BOLD response to diminish as a function of reduced mismatch between higher-level predictions and the actual sensory

input (Alink et al., 2010; Egner et al., 2010), we did not find any significant neural clusters in the EO vs NEO contrast. However, the reversed NEO vs EO contrast elicited increased neural activation in the left cerebellum, left FFG, right pmFG and parietal areas embracing the bilateral precunei. Here, given an outcome that contradicted the predictions about the presence or absence of agent B, cerebellar and parietal activations are in agreement with cumulated evidence supporting the importance of cerebello-cortical contributions in the computation of error signals (Sokolov et al., 2017). Likewise, activation in the left FFG and the pmFG have previously been related to incongruent contrasted to congruent pairs of stimuli (Cieslik et al., 2015; Quadflieg et al., 2015).

Third, in a regression analysis, we demonstrated that neural activation in the left amygdala during task contrasted to baseline negatively correlated with participant-specific sensitivity d' . Therefore, activation in the amygdala decreased with increasing perceptual ability to discriminate between Signal and Noise. In line with our expectations of neural correlates involved in higher-order computations, the amygdala has been portrayed as functional node between bottom-up driven perception and top-down predictions (Bzdok et al., 2013). Additionally, evidence points toward the amygdala's role of adjusting attentional foci and motor responses in correspondence with the assigned salience and relevance of stimuli for a specific task (Adolphs, 2010). Consequently, higher involvement of the amygdala might indicate difficulties in coordinating stimulus-oriented and stimulus-independent processing, which results in a reduced ability to discriminate between Signal and Noise. Concerning the second regression analysis, we did not find any neural correlates of criterion c values. Here, in light of the small sample size of $N = 27$, the method used might not have provided enough statistical power to reveal a small correlational effect (Cremers et al., 2017).

By means of a psychophysiological interaction analysis, we investigated the functional connectivity of the amygdala. In the context of individual compared to communicative actions, the amygdala was more functionally coupled to a fronto-parietal network that had already been observed during the task > baseline contrast and the main effect of individual vs communicative actions and that is known to emerge in tasks that require executive control to enable action processing and biological motion perception (Caspers et al., 2010; Rottschy et al., 2012; Pavlova, 2012). In conformity with this finding, the amygdala also co-activated with the inferior temporal gyri, which are thought to be important in early visual motion processing contributing to the recognition of meaningful figures (Peuskens et al., 2005; Jastorff and Orban, 2009). Additional co-activation was found in the cerebellum, an area known to contribute to inhibitory motor control (Picazio and Koch, 2015). Conversely, in the context of communicative actions, the amygdala was coupled to the left Tp as well as extensive regions in the superior medial gyrus, orbitofrontal gyrus and anterior cingulate cortex, which we will refer to as mPFC. Both the left Tp and the mPFC have been deemed critical for complex social inference (Amodio and Frith, 2006; Cohn et al., 2015; Yang et al., 2015). Thus, although both communicative and individual point-light actors create a social context, only during communicative trials, the amygdala increases its functional coupling to brain areas implicated in mentalizing. In light of the fast and automatic nature of amygdala functioning in social cognition (Satpute and Lieberman, 2006), our findings indicate that the amygdala might play a calibrating role in adapting to the specific social context either being

predictive or non-predictive. Given the negative relationship of sensitivity d' and neural activation in the amygdala, the psychophysiological interaction analysis shows two antithetical modes of perceptual decrement. In a context of individual actions, high joint activation of fronto-parietal regions, the inferior temporal gyri and thalami potentially reflects high-task demands whereas in a context of communicative actions, the amygdala may promote the integration of mentalizing-based computations.

Conclusions

Taken together, our findings indicate a neural representation of predictions drawn from communicative actions. More specifically, we showed that the right SFG and an action observation network were responsive to the violation of predictions. Moreover, reduced activation in the action observation network after communicative actions might further reflect a decreased need for executive control in order to meet the perceptual demands of the task. Amygdala signaling, however, was associated with decreased overall perceptual sensitivity. Pivotal, in the context of communicative actions, the amygdala increased its functional coupling to mPFC, an area known to be involved in mentalizing processes. Future studies shall deepen our understanding of IPPC by manipulating the probability of FA responses, namely the perception of the so-called 'Bayesian ghost' (Manera et al., 2011c), while controlling for confounding effects due to a change in the experimental setting.

Supplementary data

Supplementary data are available at SCAN online.

Conflict of interest. None declared.

Funding

L.S. was supported by a grant for an Independent Max Planck Research Group; C.B. was supported by the European Research Council under the European Union's Seventh Framework Programme (FP/2007-2013)/European Research Council Grant Agreement.

References

- Adolphs, R. (2010). What does the amygdala contribute to social cognition. *Annals of the New York Academy of Sciences*, **1191**, 42–61.
- Alink, A., Schwiedrzik, C.M., Kohler, A., et al. (2010). Stimulus predictability reduces responses in primary visual cortex. *Journal of Neuroscience*, **30**, 2960–6.
- Amodio, D.M., Frith, C.D. (2006). Meeting of minds: the medial frontal cortex and social cognition. *Nature Reviews Neuroscience*, **7**, 268–77.
- Barbey, A.K., Krueger, F., Grafman, J. (2009). Structured event complexes in the medial prefrontal cortex support counterfactual representations for future planning. *Philosophical Transactions of the Royal Society, B: Biological Sciences*, **364**, 1291–300.
- Becchio, C., Manera, V., Sartori, L., et al. (2012). Grasping intentions: from thought experiments to empirical evidence. *Frontiers in Human Neuroscience*, **6**, 117.

- Bludau, S., Eickhoff, S.B., Mohlberg, H., et al. (2014). Cytoarchitecture, probability maps and functions of the human frontal pole. *NeuroImage*, *93*(Pt 2), 260–75.
- Brainard, D.H. (1997). The psychophysics toolbox. *Spatial Vision*, *10*, 433–6.
- Brett, M., Anton, J., Valabregue, R., et al. (2002). Region of interest analysis using an SPM toolbox. In: *8th International Conference on Functional Mapping of the Human Brain, Sendai, Japan, 2–6 June 2002*[Abstract] available on CD-ROM in *NeuroImage*, Vol 16, No 2.
- Burr, D.C., Neri, P., Morrone, M.C. (1998). Seeing biological motion. *Nature*, *395*, 894–6.
- Bzdok, D., Laird, A.R., Zilles, K., et al. (2013). An investigation of the structural, connectional, and functional subspecialization in the human amygdala. *Human Brain Mapping*, *34*, 3247–66.
- Caballero-Gaudes, C., Reynolds, R.C. (2017). Methods for cleaning the BOLD fMRI signal. *NeuroImage*, *154*, 128–49.
- Caspers, S., Zilles, K., Laird, A.R., et al. (2010). ALE meta-analysis of action observation and imitation in the human brain. *NeuroImage*, *50*, 1148–67.
- Cieslik, E.C., Mueller, V.I., Eickhoff, C.R., et al. (2015). Three key regions for supervisory attentional control: evidence from neuroimaging meta-analyses. *Neuroscience and Biobehavioral Reviews*, *48*, 22–34.
- Cohn, M., St-Laurent, M., Barnett, A., et al. (2015). Social inference deficits in temporal lobe epilepsy and lobectomy: risk factors and neural substrates. *Social Cognitive and Affective Neuroscience*, *10*, 636–44.
- Cremers, H.R., Wager, T.D., Yarkoni, T., et al. (2017). The relation between statistical power and inference in fMRI. *PLoS One*, *12*, e0184923.
- Egner, T., Monti, J.M., Summerfield, C. (2010). Expectation and surprise determine neural population responses in the ventral visual stream. *Journal of Neuroscience*, *30*, 16601–16608.
- Eickhoff, S.B., Stephan, K.E., Mohlberg, H., et al. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage*, *25*, 1325–35.
- Friston, K. (2002). Functional integration and inference in the brain. *Progress in Neurobiology*, *68*, 113–43.
- Heleven, E., Van Overwalle, F. (2016). The person within: memory codes for persons and traits using fMRI repetition suppression. *Social Cognitive and Affective Neuroscience*, *11*, 159–71.
- Henson, R. (2007). Efficient experimental design for fMRI. In: Penny, W., Friston, K., Ashburner, J., et al., editors. *Statistical Parametric Mapping: The Analysis of Functional Brain Images*, London: Elsevier, 193–210.
- Jastorff, J., Orban, G.A. (2009). Human functional magnetic resonance imaging reveals separation and integration of shape and motion cues in biological motion processing. *Journal of Neuroscience*, *29*, 7315–29.
- van Kemenade, B.M., Muggleton, N., Walsh, V., et al. (2012). Effects of TMS over premotor and superior temporal cortices on biological motion perception. *Journal of Cognitive Neuroscience*, *24*, 896–904.
- Kiebel, S., Holmes, A. (2004). The general linear model. In: Frackowiak, K., Friston, K., Frith, C., et al., editors. *Human Brain Function 2*, London: Elsevier, 725–60.
- Kleiner, M., Brainard, D., Pelli, D., et al. (2007). What's new in psychtoolbox-3. *Perception*, *36*, 1–16.
- Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Frontiers in Psychology*, *4*, 863.
- von der Lühse, T., Manera, V., Barisic, I., et al. (2016). Interpersonal predictive coding, not action perception, is impaired in autism. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *371*, 20150373.
- Majerus, S., Péters, F., Bouffier, M., et al. (2018). The dorsal attention network reflects both encoding load and top-down control during working memory. *Journal of Cognitive Neuroscience*, *30*, 144–59.
- Manera, V., Becchio, C., Cavallo, A., et al. (2011a). Cooperation or competition? Discriminating between social intentions by observing prehensile movements. *Experimental Brain Research*, *211*, 547–56.
- Manera, V., Becchio, C., Schouten, B., et al. (2011b). Communicative interactions improve visual detection of biological motion. *PLoS One*, *6*, e14594.
- Manera, V., Del Giudice, M., Bara, B.G., et al. (2011c). The second-agent effect: communicative gestures increase the likelihood of perceiving a second agent. *PLoS One*, *6*, e22650.
- Manera, V., Schouten, B., Becchio, C., et al. (2010). Inferring intentions from biological motion: a stimulus set of point-light communicative interactions. *Behavior Research Methods*, *42*, 168–78.
- Manera, V., Schouten, B., Verfaillie, K., et al. (2013). Time will show: real time predictions during interpersonal action perception. *PLoS One*, *8*, e54949.
- Marsh, K.L., Richardson, M.J., Schmidt, R.C. (2009). Social connection through joint action and interpersonal coordination. *Topics in Cognitive Science*, *1*, 320–39.
- McLaren, D.G., Ries, M.L., Xu, G., et al. (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. *NeuroImage*, *61*, 1277–86.
- Mueller-Putz, G., Scherer, R., Brunner, C., et al. (2008). Better than random: a closer look on BCI results. *International Journal of Bioelectromagnetism*, *10*, 52–5.
- Neri, P., Luu, J.Y., Levi, D.M. (2006). Meaningful interactions can enhance visual discrimination of human agents. *Nature Neuroscience*, *9*, 1186–92.
- Okruszek, Ł., P, A., Wysokiński, A., et al. (2017). The second agent effect: interpersonal predictive coding in people with schizophrenia. *Social Neuroscience*, 1–6.
- Oldfield, R.C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, *9*, 97–113.
- Pavlova, M.A. (2012). Biological motion processing as a hallmark of social cognition. *Cerebral Cortex*, *22*, 981–95.
- Peuskens, H., Vanrie, J., Verfaillie, K., et al. (2005). Specificity of regions processing biological motion. *European Journal of Neuroscience*, *21*, 2864–75.
- van Pelt, S., Heil, L., Kwisthout, J., et al. (2016). Beta- and gamma-band activity reflect predictive coding in the processing of causal events. *Social Cognitive and Affective Neuroscience*, *11*, 973–80.
- Picazio, S., Koch, G. (2015). Is motor inhibition mediated by cerebello-cortical interactions. *Cerebellum*, *14*, 47–9.
- Quadflieg, S., Gentile, F., Rossion, B. (2015). The neural basis of perceiving person interactions. *Cortex*, *70*, 5–20.
- Rorden, C., Brett, M. (2000). Stereotaxic display of brain lesions. *Behavioural Neurology*, *12*, 191–200.
- Rottschy, C., Langner, R., Dogan, I., et al. (2012). Modelling neural correlates of working memory: a coordinate-based meta-analysis. *NeuroImage*, *60*, 830–46.
- Sapey-Triomphe, L.-A., Centelles, L., Roth, M., et al. (2016). Deciphering human motion to discriminate social interactions: a developmental neuroimaging study. *Social Cognitive and Affective Neuroscience*, *12*, 340–51.
- Satpute, A.B., Lieberman, M.D. (2006). Integrating automatic and controlled processes into neurocognitive models of social cognition. *Brain Research*, *1079*, 86–97.

- Saygin, A.P., Wilson, S.M., Hagler, D.J., et al. (2004). Point-light biological motion perception activates human premotor cortex. *Journal of Neuroscience*, *24*, 6181–8.
- Sokolov, A.A., Miall, R.C., Ivry, R.B. (2017). The cerebellum: adaptive prediction for movement and cognition. *Trends in Cognitive Sciences*, *21*, 313–32.
- Stanislaw, H., Todorov, N. (1999). Calculation of signal detection theory measures. *Behavior Research Methods, Instruments, & Computers*, *31*, 137–49.
- Underwood, A.G., Gynn, M.J., Cohen, A.-L. (2015). The future orientation of past memory: the role of BA 10 in prospective and retrospective retrieval modes. *Frontiers in Human Neuroscience*, *9*, 668.
- Vossel, S., Weidner, R., Driver, J., et al. (2012). Deconstructing the architecture of dorsal and ventral attention systems with dynamic causal modeling. *The Journal of Neuroscience*, *32*, 10637–10648.
- Wood, J.N., Knutson, K.M., Grafman, J. (2004). Psychological structure and neural correlates of event knowledge. *Cerebral Cortex*, *15*, 1155–61.
- Yang, D.Y.-J., Rosenblau, G., Keifer, C., et al. (2015). An integrative neural model of social perception, action observation, and theory of mind. *Neuroscience and Biobehavioral Reviews*, *51*, 263–75.
- Yarkoni, T., Poldrack, R.A., Nichols, T.E., et al. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods*, *8*, 665–70.

3 Direct Gaze and Action Control

3.1 Summary

In order to shed light on action control processes during the direct experience of social signals, the second study of this thesis (Zillekens, Schliephake, Brandi, & Schilbach, 2019) addressed the interaction of gaze processing and spatial action congruency for complementary motor reactions from a second-person perspective. More specifically, moving beyond mere imitation, we investigated the behavioral and BOLD correlates of spatially congruent vs. incongruent button presses to direct vs. averted gaze movements displayed by a same-sex anthropomorphic virtual character. After completing the AQ questionnaire (Baron-Cohen, Wheelwright, Skinner, et al., 2001) 30 healthy participants performed a spatial stimulus-response compatibility task while lying in an fMRI scanner. On the behavioral level, RT costs for incongruent vs. congruent reactions (RT incongruency costs), did not differ between the direct and the averted gaze condition. Similarly, there was no significant BOLD interaction effect of gaze and congruency. However, in line with previous findings of a behavioral insensitivity to direct gaze stimuli in a sample of autistic individuals (Schilbach et al., 2012), we showed that participants with less pronounced autistic traits had higher RT incongruency costs in the direct as compared to the averted gaze condition whereas participants with more strongly pronounced autistic traits demonstrated higher RT incongruency costs in the averted as compared to the direct gaze condition. This result indicates a decreasing sensitivity to direct gaze stimuli with increasing autistic traits and underlines the dependency between social interactive signals and action control processes. In order to concretely study the interaction-dependent integration of gaze and action control processes, we focused on the connectivity alterations in the right TPJ, which has been described as the core gaze processing region (Haxby, Hoffman, & Gobbini, 2000; Schobert, Corradi-Dell'Acqua, Frühholz, van der Zwaag, & Vuilleumier, 2018) and which is characterized by multimodal functional brain connections (Bzdok, Langner, et al., 2013) as well as gaze-dependent functional connectivity patterns (Nummenmaa, Passamonti, Rowe, Engell, & Calder, 2010). By conducting a psychophysiological interaction analysis, we analyzed the context-dependent functional connectivity of a right TPJ seed with an "action network", both derived from meta-analytical probability maps from Neurosynth (Yarkoni et al., 2011). Our results demonstrate an increased functional coupling between the right TPJ and the inferior frontal gyrus, a brain region relevant both for motor inhibition and social cognition (Chen et al., 2018; Schulz et al., 2009; Zhang, Geng, & Lee, 2017), in the context of incongruency costs to direct as compared to averted gaze movements. Contrarily, in

the context of incongruency costs for averted as compared to direct gaze movements, the right TPJ showed increased functional connectivity with primarily left-hemispheric areas of the action network that have been associated with attentional control processes (Corbetta & Shulman, 2002; Vossel et al., 2012). The findings support theories suggesting a decisive role of direct gaze stimuli in social cognition (Senju & Johnson, 2009b) and a multimodal functional integration via the gaze-sensitive right TPJ (Bzdok, Langner, et al., 2013), functionally connecting an action network with areas involved in mentalizing (Ciaramidaro, Becchio, Colle, Bara, & Walter, 2014).

3.2 Contributions and reference

The study “A look at actions: Direct gaze modulates functional connectivity of the right TPJ with an action control network” was published in *Social Cognitive and Affective Neuroscience* in 2019. The project was supervised by ML. B. and L.S. Research and stimuli design was performed by L.M.S. and ML.B. I.C.Z., L.M.S. and ML.B. were involved in programming and data collection. Data were analyzed by I.C.Z., L.M.S. and ML.B. The manuscript was written by I.C.Z. All authors reviewed and edited the manuscript. Funding was provided by L.S.

Zillekens, I. C., Schliephake, L. M., Brandi, M.-L, & Schilbach, L. (2019). A look at actions: Direct gaze modulates functional connectivity of the right TPJ with an action control network. *Social Cognitive and Affective Neuroscience*. (Advance online publication. doi:10.1093/scan/nsz071)

A look at actions: direct gaze modulates functional connectivity of the right TPJ with an action control network

Imme Christina Zillekens,^{1,2} Lena Maria Schliephake,³ Marie-Luise Brandi,¹ and Leonhard Schilbach^{1,2,4,5}

¹ Independent Max Planck Research Group for Social Neuroscience, Max Planck Institute of Psychiatry, Munich, Germany ²International Max Planck Research School for Translational Psychiatry (IMPRS-TP), Munich, Germany ³Institute for Psychology, University of Münster, Münster, Nordrhein-Westfalen, Germany ⁴Department of Psychiatry, Ludwig-Maximilians-Universität, Munich, Germany ⁵Outpatient and Day Clinic for Disorders of Social Interaction, Max Planck Institute of Psychiatry, Munich, Germany

Correspondence should be addressed to Imme Christina Zillekens, Max Planck Institute of Psychiatry, Kraepelinstr. 2-10, 80804 Munich, Germany.
E-mail: imme_zillekens@psych.mpg.de

Abstract

Social signals such as eye contact and motor actions are essential elements of social interactions. However, our knowledge about the interplay of gaze signals and the control of actions remains limited. In a group of 30 healthy participants, we investigated the effect of gaze (direct gaze vs averted) on behavioral and neural measures of action control as assessed by a spatial congruency task (spatially congruent vs incongruent button presses in response to gaze shifts). Behavioral results demonstrate that inter-individual differences in condition-specific incongruency costs were associated with autistic traits. While there was no interaction effect of gaze and action control on brain activation, in a context of incongruent responses to direct gaze shifts, a psychophysiological interaction analysis showed increased functional coupling between the right temporoparietal junction, a key region in gaze processing, and the inferior frontal gyri, which have been related to both social cognition and motor inhibition. Conversely, incongruency costs to averted gaze were reflected in increased connectivity with action control areas implicated in top-down attentional processes. Our findings indicate that direct gaze perception inter-individually modulates motor actions and enforces the functional integration of gaze-related social cognition and action control processes, thereby connecting functional elements of social interactions.

Key words: direct gaze; action control network; spatial compatibility; fMRI; connectivity

Introduction

The interdependency of gaze processing and motor actions plays a key role in our everyday social interactions. Underlining their joint functioning, empirical studies have revealed a strong overlap between brain areas that process hand and gaze movements

(e.g. Pierno *et al.*, 2006). Furthermore, it has been shown that social gaze impacts goal-directed movement precision (Becchio *et al.*, 2008) as well as reaction speed (Hietanen *et al.*, 2006; Schilbach *et al.*, 2011). The latter, however, could not be observed in individuals with autism spectrum disorder (Schilbach *et al.*, 2012), who are also characterized by abnormalities in motor

Received: 9 April 2019; Revised: 11 June 2019; Accepted: 19 August 2019

© The Author(s) 2019. Published by Oxford University Press.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

behaviors as well as the processing of eyes and observed movements (Marsh and Hamilton, 2011; Tanaka and Sung, 2016).

In social interactions, a specific role needs to be attributed to the perception of direct gaze, which reflexively attracts attention (Friesen and Kingstone, 1998; Bristow et al., 2007). Crucially, direct as compared to averted gaze has been described as a signal that conveys the intention to interact (Senju and Johnson, 2009). In line with this, empirical evidence suggests a facilitation effect of direct gaze on imitative behavior (Wang et al., 2011a; Prinsen et al., 2017) as well as an attentional effect of gaze cues on manual responses to target stimuli (Bristow et al., 2007; Böckler et al., 2014). Yet, besides imitation and beyond attentional guidance of gaze, social interactions might require re-actions to gaze movements that are compatible but not identical with observed actions (Schilbach et al., 2013). Still, how gaze interacts with action control processes on the behavioral and brain level and how the specific gaze context modulates functional connectivity between gaze and action control areas, particularly when tendencies towards spatial congruency need to be suppressed, remains unclear. Therefore, we systematically investigated how the perception of direct or averted gaze affects action control in the context of an fMRI-compatible and previously established spatial stimulus-response compatibility (SSRC) paradigm (Schilbach et al., 2011; Schilbach et al., 2012). Instead of using social and non-social stimuli as in previous studies, we realized a 2 × 2 factorial design by asking participants to generate button presses in a spatially congruent or incongruent manner (factor congruency: CON vs INCON) in response to gaze shifts produced by an anthropomorphic virtual character (VC), whose initial gaze position was either direct or averted (factor gaze: direct vs averted). As dependent variables, we measured task performance (accuracy) and reaction time (RT) as well as brain activity obtained via BOLD fMRI.

In line with empirical evidence, incongruent compared to congruent reactions incur increased computational load and thus, lead to prolonged RTs and a decreased percentage of correct responses (Iacoboni et al., 1996; Hietanen et al., 2006). Additionally, the incongruency effect should be reflected in an increased activation in a bilateral dorsal fronto-parietal network of frontal motor areas and superior parietal lobules, a network responsive to increased top-down attentional demands and need for increased action control (Corbetta and Shulman, 2002; Cieslik et al., 2015). For the main effect of direct compared to averted gaze, we hypothesized brain regions sensitive to eye contact and gaze-related movements (Haxby et al., 2000; Schobert et al., 2018), namely the temporoparietal junction/posterior sulcus temporalis superior (TPJ/pSTS) and the fusiform gyrus, to show increased BOLD signal in response to direct gaze stimuli (Calder et al., 2002; Pelphrey et al., 2003; Senju and Johnson, 2009).

The main focus of this study was to investigate the interaction between the perception of gaze and mechanisms of action control. While some evidence suggests a general facilitation effect of direct gaze (Schilbach et al., 2011, 2012), in other studies, an association of direct gaze and accelerated reactions has only been found for compatible stimulus-response mappings (Bristow et al., 2007; Böckler et al., 2014; Prinsen et al., 2017). On the brain level, both motor control areas such as the inferior frontal cortex as well as the gaze sensitive TPJ have been implicated in the interaction of gaze and motor control processes (Schilbach et al., 2011; Wang et al., 2011b). Building on this, the present study tested whether the same brain regions are differentially recruited as representations of gaze-dependent incongruency costs. Furthermore, in light of evidence that indicates gaze-dependent functional connectivity changes of the

TPJ/pSTS with an extended gaze perception network (Nummenmaa et al., 2010) as well as multi-modal functional coupling of the right TPJ (Bzdok et al., 2013), we expected gaze and action control networks to interact at the level of right TPJ connectivity, reflecting a differential integration of gaze-related and action control processes. Thus, in order to systematically investigate the relationship of gaze-specific incongruency costs in terms of functional connectivity, we conducted a psychophysiological interaction analysis and analyzed whether the interplay of the gaze context and action control demands modulates the functional connectivity between the right TPJ and an 'action control network', being composed of all action-associated brain regions as defined by a Neurosynth (Yarkoni et al., 2011) search including the search term 'action'. In a context of direct gaze and an increased demand for action inhibition due to spatial incongruence, we expected to see increased functional coupling between our seed region, which was located in a functional cluster that has been related to social cognition (Bzdok et al., 2013), and particularly the IFG, indicating an integration of gaze-related social cognition and action control (Schilbach et al., 2011; Wang and Hamilton, 2012; Callejas et al., 2014).

In light of autism-related differences observed in the original version of our SSRC task (Schilbach et al., 2012), we further obtained measures of autistic traits and hypothesized to replicate a positive relationship between autistic traits and gaze-specific incongruency costs.

Methods

Thirty-two volunteers (15 females) participated in our study. Due to neurological and psychiatric conditions (sleeping disorder, ventriculomegaly), two participants were excluded from all further analyses. The remaining 30 participants (14 females) had a mean age of 24 (s.d. = 5.08, range = 19–41), normal or corrected-to-normal vision, no history of neurological or psychiatric history and were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). The mean group autism quotient (AQ) (Baron-Cohen et al., 2001) was 14.99 (s.d. = 6.38, range = [6, 32]). All participants gave informed written consent and received a fixed monetary compensation of 30€. At the end of the experiment, participants were debriefed and thanked for their participation. The study protocol followed the guidelines of the Declaration of Helsinki and was approved by the ethics committee of the Ludwig-Maximilians-Universität München.

Experimental design and procedure

The paradigm used in this fMRI study resembled an adapted version of previously used SSRC paradigm (Schilbach et al., 2011; Schilbach et al., 2012). Instead of asking participants to respond to the gaze movement of an anthropomorphic VC or the movement of a geometric symbol as in previous studies, VCs were always present. This allowed us to keep the social stimulus constant while now systematically manipulating exposures to direct compared to averted gaze.

Before the experiment and before entering the fMRI scanner, participants received detailed instructions on the overall procedure and MRI safety. During the experiment, they were asked to respond as fast as possible to gaze shifts shown by the VC by pressing a right or left button using the right or left index finger, respectively. The experiment consisted of 24 blocks of 12 events each with 50% left- and 50% right-directional gaze shifts, realizing a 2 × 2 factorial design: congruent blocks were instructed by the initial cue 'GLEICH' (German for 'same') and required

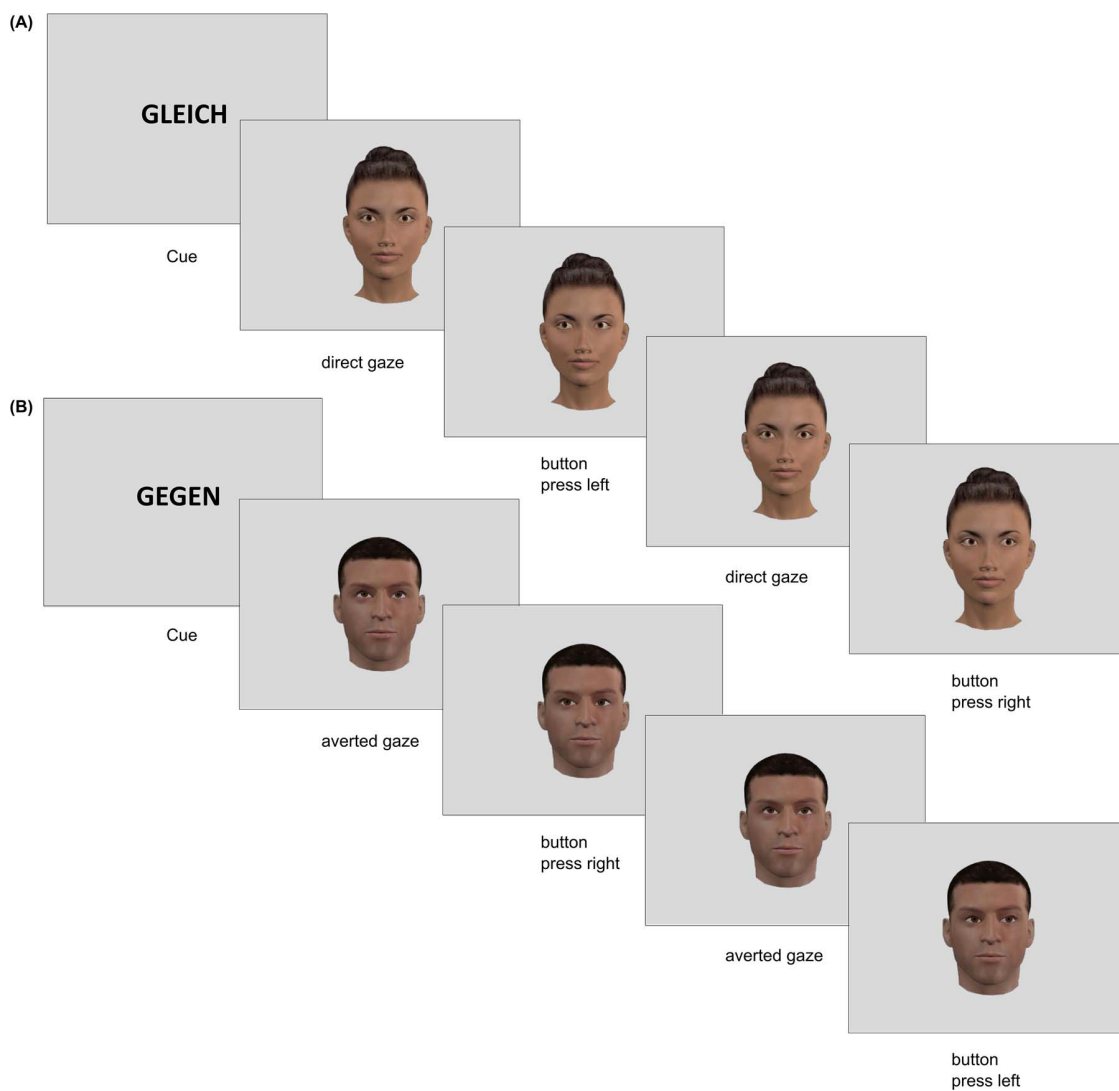


Fig. 1. Experimental task. (A) One of two female VCs demonstrating direct gaze in the congruent condition [indicated by the initial cue 'GLEICH' (German for 'same')]. The first gaze shift to the left requires a congruent left button press, the second gaze shift to the right a right button press. (B) One of two male VCs demonstrating averted gaze in the incongruent condition [indicated by the initial cue 'GEGEN' (German for 'opposite')]. The first gaze shift to the left requires an incongruent right button press, the second gaze shift to the right a left button press.

participants to respond to gaze shifts in a spatially compatible manner, i.e. pressing the ipsilateral button. The initial cue 'GEGEN' (German for 'opposite') introduced blocks of spatially incompatible responses, where participants had to press the contralateral button in response to a gaze shift, for instance the right button had to be pressed following a gaze shift to the left (Figure 1). Each cue was presented once for 1500 ms at the beginning of each block of 12 gaze shifts and each block was followed by a jittered inter-stimulus interval of 15 to 17 s. During the experiment, participants did not receive any feedback on their performance. Besides the factor 'congruency', our second experimental factor 'gaze' was expressed by the VC either looking up (averted gaze) or facing the participant (direct gaze). Pixel coordinates and the timing of gaze shifts were identical over all conditions. In each block, male participants experienced one of two male VCs while female participants were confronted with one of two female VCs. The appearance of either of the two same sex VCs was equally likely. Stimuli

were presented through the software package Presentation (Neurobehavioral Systems, Inc.; Version 18.1) on an fMRI compatible computer monitor (refresh rate = 59 Hz, resolution of 1024×768 , viewable region of $500 \text{ mm} \times 380 \text{ mm}$) and were created manually in Poser 10 (Smith Micro Software, Inc., CA, USA). As stimuli of the present study differed from stimuli of previous studies, a pre-study was conducted to control for unbalanced stimuli preferences. Twelve volunteers (employees, 8 females) from the Max Planck Institute of Psychiatry rated all four VCs on a five-level Likert scale on attractiveness, valence, arousal and other characteristics (Supplementary Table S1). A repeated measures ANOVA using stimulus type (VC 1–4) and characteristics (Supplementary Table S1) revealed no significant effect of stimulus type ($F(1,11) = 0.94$, $P = 0.43$) or interaction effect on VC ratings, $F(1,11) = 1.15$, $P = 0.10$. All volunteers correctly indicated whether the VC demonstrated direct or averted gaze and whether the gaze was directed to the left or right.

Behavioral and questionnaire data preprocessing

RTs, the dependent variable that expressed the behavioral outcome of action control, reflected the time frame between the onset of the gaze shift and the button press of the participant. We applied the following RT data preprocessing steps (e.g. Engell *et al.*, 2010; Böckler *et al.*, 2014): trials with no answer, multiple answers or incorrect answers were categorized as error trials. Further, trials with responses two standard deviations from the participant-specific mean RT over all conditions were interpreted as anticipation error or missed response and also labeled as error trials. In total, 9.4% of all trials were error trials. In order to exclude uninformative task blocks, e.g. blocks in which participants missed the initial instructive cue, blocks with more than 25% error trials ($>=3$ error trials/block) were not considered in subsequent analyses, resulting in an average exclusion of one block per participant (Supplementary Table S2 for details). Task performance reflected the mean percentage of correctly answered trials of all correct and error trials, which was calculated for each combination of experimental conditions. The AQ of participants was assessed in order to evaluate the relationship of autistic traits and gaze-specific incongruency costs. To conserve comparability of AQ scores, missing values (four participants did not fill in one item each) were interpolated over the individual sub-scale values of the respective item filling in the missing data point.

Behavioral data analyses

Main effects and interaction effects of experimental conditions on task performance and RTs were tested by means of repeated measures 2 (gaze: direct vs averted) \times 2 (congruency: congruent vs incongruent) ANOVAs. To test whether direct gaze modulates responses in the congruent or incongruent condition, we implemented post-hoc contrasts of conditions (direct_CON vs averted_CON; direct_INCON vs averted_INCON) as Bonferroni corrected paired two-sided *t*-tests. After calculating the RT incongruency costs, i.e. RT slowing in incongruent compared to congruent trials, we obtained the difference in RT incongruency costs between the direct and averted gaze condition (incongruency costs direct—incongruency costs averted) as a measure of direction and size of effect of gaze on RT incongruency costs. To further analyze the relationship of the difference in RT incongruency costs between the direct and the averted gaze condition, we correlated the measure with AQ scores. Here, due to non-normally distributed AQ scores (Shapiro–Wilk statistic = 0.93, $P < 0.05$), the non-parametric two-sided Spearman's rank correlation statistic was used.

fMRI data analysis

Participants completed the experiment inside a 3T MR scanner (MR750, GE, Milwaukee, USA). The procedure comprised a single functional run of 290 volumes of 40 slices (32-channel head coil, AC-PC-orientation, 96×96 matrix, 3×3 mm voxel size, 3 mm slice thickness, 0.5 mm slice gap). First, structural T1-weighted images were acquired [BRAVO FSPGR pulse sequence, 1 mm isotropic voxels, repetition time (TR) of 6.2 ms, echo time (TE) of 2.3 ms]. Second, during the experiment, T2*-weighted functional images were obtained by means of gradient echo planar imaging (TR of 2000 ms, TE of 20 ms, 90° flip angle) and the first four functional volumes were removed to control for non-equilibrium effects. fMRI data preprocessing and analysis were performed in SPM12 (Statistical Parametric Mapping Software, Wellcome Department of Imaging Neuroscience,

London; <http://www.fil.ion.ucl.ac.uk>) and included the following steps: functional images were spatially realigned to the mean functional image (rigid body transformation). Next, functional and structural images were co-registered. Both structural and functional images were spatially normalized to the Montreal Neurological Institute (MNI) template using tissue segmented T1-weighted anatomical images (BRAVO FSPGR pulse sequence, 1 mm isotropic voxels, TR of 6.2 ms, TE of 2.3 ms). Functional images were resliced to $2 \times 2 \times 2$ mm voxel size. Finally, a 3D Gaussian Kernel with full width of half maximum of 8 mm was used for smoothing.

All valid experimental blocks (RT data preprocessing) were modeled as epochs in a general linear model (GLM) with an average duration of 54 s (range 46–64 s). Experimental factors, i.e. 'gaze' (direct vs averted gaze) and 'congruency' (congruent vs incongruent) were captured in four different regressors of interest. Error blocks were modeled by a regressor of no interest. Our GLM design matrix further contained 26 confound regressors of no interest: the first 24 contained six z-standardized rigid body motion realignment parameters, their temporal derivatives and the squared values of both realignment parameters and derivatives (Friston *et al.*, 1996). Another two regressors captured confounding signal from white matter and cerebrospinal fluid. Here, we obtained a binarized mask from the respective segmented individual structural images using a 0.95 threshold in SPM's image calculator (imcalc tool) and calculated the first principal component of the respective tissue type, explaining 85.42% (s.d. = 4.28%) and 79.11% (s.d. = 5.85%) of variance in the signal (Caballero-Gaudes and Reynolds, 2017). No global scaling was applied and low-frequency signal drifts were filtered out (128 s cutoff period). In order to correct for temporal autocorrelation of the data, voxel-wise maximum likelihood estimators were calculated (Kiebel and Holmes, 2004).

Studying the effect of congruency and gaze as well as their interaction, BOLD signal during main effects and interactions of conditions were analyzed in a second-level flexible factorial design. A binarized group-specific explicit grey matter (GM) mask (sum of participant specific probability of $GM > 0.05$; imcalc tool) contained all voxels of interest. Besides our two experimental factors, we added a 'subject' factor, accounting for subject-specific heteroscedasticity, and implemented SPM's default settings of unequal variances within each factor. In order to analyze the main effects of congruency and gaze, we contrasted congruent and incongruent as well as direct and averted gaze conditions [congruency: (direct_CON + averted_CON) > (direct_INCON + averted_INCON), (direct_INCON + averted_INCON) > (direct_CON + averted_CON); gaze: (direct_CON + direct_INCON) > (averted_CON + averted_INCON), (averted_CON + averted_INCON) > (direct_CON + direct_INCON)]. Statistical interactions of conditions were modeled as contrast of incongruency costs in the direct and averted gaze conditions [IA1: (direct_INCON > direct_CON) > (averted_INCON > averted_CON), IA2: (averted_INCON > averted_CON) > (direct_INCON > direct_CON)].

Moreover, we conducted a generalized condition-specific psychophysiological interaction analysis (McLaren *et al.*, 2012) to investigate the context-dependent functional coupling between gaze and action processing areas. Based on the available literature and a term-based meta-analysis in Neurosynth (Yarkoni *et al.*, 2011), we identified a region typically labelled as right TPJ (Schurz *et al.*, 2017) as the seed region for our gPPI analysis. The coordinates of our seed region [$44, -52, 12$] represented the peak coordinates in the brain map of the term 'gaze' (retrieved 2 October 2018 from www.neurosynth).

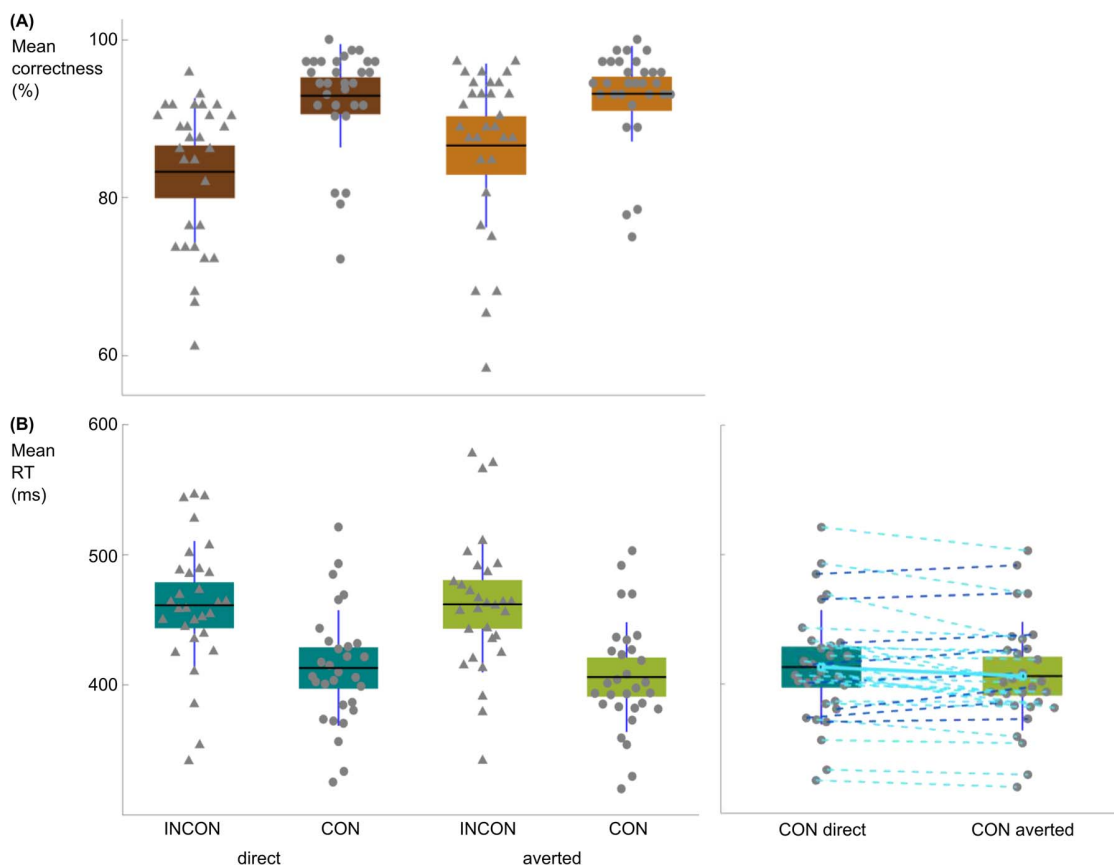


Fig. 2. Behavioral measures. (A) Mean percentage of correct responses and (B) left panel: mean RTs; right panel: mean RTs for direct and averted gaze in the congruent condition. Light blue lines mark a decrease in RT from direct to averted; dark blue lines mark an increase. The light blue solid line represents the mean decrease in RTs from the direct to the averted gaze condition. Black horizontal lines represent the mean values, boxes represent the standard error of the mean (SEM), blue vertical lines the standard deviation (s.d.).

org, z -score=7.33) and were further situated in a functional sub-section of the right TPJ involved in social cognition (Bzdok et al., 2013; Neurosynth, retrieved 3 June 2019, meta-analytic association of peak coordinates with terms ‘default network’, ‘mentalizing’). After creating a sphere of 6 mm radius in marsbar (Brett et al., 2002; Supplementary Figure S1A), we extracted the first eigenvariate of our seed sphere and allowed actual ROIs to vary in size between participants, but restricted them to first level masks generated by SPM12. In order to investigate the context-dependent functional coupling of our right TPJ seed with brain areas involved in action control, we retrieved an associative ‘action’ mask from Neurosynth (Yarkoni et al., 2011; retrieved 2 October 2018 from www.neurosynth.org). After smoothing (3D Gaussian Kernel with full width of half maximum of 4 mm) and binarization (imcalc, $i1 > 0.1$, Supplementary Figure S1B), it was implemented as explicit mask in our second level analysis. Specifically, we were interested in the functional coupling of the right TPJ and the action network for the statistical interactions of our experimental conditions [IA1: (direct_INCON > direct_CON) > (averted_INCON > averted_CON)] and [IA2: (averted_INCON > averted_CON) > (direct_INCON > direct_CON)].

Statistical maps of the activation analysis are shown at a cluster-forming threshold of $P < 0.001$ (uncorrected) and a cluster threshold of $P < 0.05$ (FWE). In the psychophysiological interaction analysis, P -values were thresholded at $P < 0.05$ (FWE) at voxel level. The Anatomy Toolbox (Eickhoff et al., 2005; Version

2.2c) and the AAL atlas in MRICron (Rorden and Brett, 2000) were used for functional localization and the Surf Ice software for brain visualizations (<https://www.nitrc.org/projects/surface/>).

Results

Behavioral results

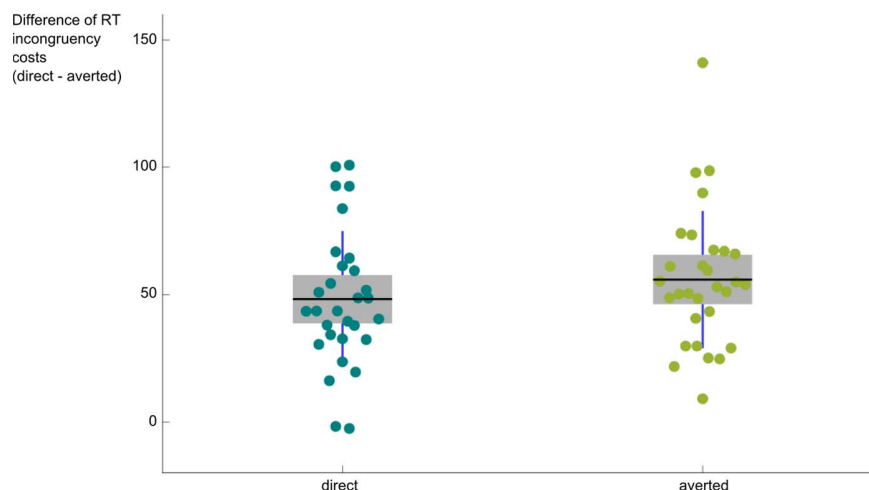
As expected, a repeated measures ANOVA focusing on the condition-specific performance revealed a significant main effect of congruency on the percentage of correct responses, $F(29,1) = 32.09$, $P < 0.001$, $\eta_p^2 = 0.53$. There was no main effect of gaze [$F(29,1) = 1.80$, $P = 0.19$, $\eta_p^2 = 0.06$] or an interaction effect of congruency and gaze on performance, $F(29,1) = 1.27$, $P = 0.27$, $\eta_p^2 = 0.04$ (Figure 2A).

A second repeated measures ANOVA demonstrated a significant main effect of congruency also on RTs, $F(29,1) = 134.71$, $P < 0.001$, $\eta_p^2 = 0.82$. Neither did gaze impact participants’ RTs [$F(29,1) = 1.30$, $P = 0.26$, $\eta_p^2 = 0.04$] nor did the interaction effect of experimental conditions reach significance, $F(29,1) = 3.88$, $P = 0.06$, $\eta_p^2 = 0.12$ (Figure 2B). Post-hoc contrasts showed that congruent RTs were significantly higher in the direct gaze compared to the averted gaze condition, $t(29) = 2.86$, $P < 0.01$, $R^2 = 0.22$. Incongruent RTs, however, did not differ between gaze conditions, $t(29) = 0.17$, $P = 0.87$. Table 1 presents the condition-specific performance and RTs.

Condition-specific RT incongruency costs, i.e. the increase in RTs in incongruent compared to congruent trials, are displayed

Table 1. Condition-specific RTs and accuracy. Brackets contain the standard deviation (s.d.).

Gaze condition	Experimental condition	Mean RT	Mean performance (percentage of correct trials)
Direct	Congruent	412.79 (44.35)	92.87 (6.53)
	Incongruent	461.02 (49.37)	83.24 (9.33)
Averted	Congruent	405.82 (42.15)	93.13 (6.05)
	Incongruent	461.70 (52.23)	86.57 (10.36)

**Fig. 3.** Condition-specific RT incongruency costs. Boxes represent the SEM.

in **Figure 3**. On average, RTs of incongruent reactions increased by 48 ms (s.d.=27 ms) in the direct gaze condition and by 56 ms (s.d.=27 ms) in the averted gaze condition. Building on this, a two-sided Spearman's rank correlation analysis indicated a significant negative correlation between AQ scores and the difference in RT incongruency costs for direct as compared to averted gaze, $r_{s(28)} = -0.40$, $P < 0.05$ (**Figure 4**).

fMRI results

Applying a cluster-forming threshold of $P < 0.001$ (uncorrected) and a cluster threshold of $P < 0.05$ (FWE), incongruent contrasted to congruent trials [(direct_INCON + averted_INCON) > (direct_CON + averted_CON)] were associated with a differential increase in BOLD signal in the right inferior parietal lobule, left superior parietal lobule and right middle frontal gyrus (**Figure 5A**). For the reversed contrast [(direct_CON + averted_CON) > (direct_INCON + averted_INCON)], a large cluster of 2319 voxels emerged in the bilateral medial prefrontal cortex (MPFC), including voxels in the superior medial gyri, superior frontal gyri and the anterior cingulate cortices, spreading to the right medial cingulate cortex. Congruent compared to incongruent trials further elicited activation in the right IFG as well as the left cerebellum and posterior part of the left fusiform gyrus (**Figure 5B**).

During direct gaze vs averted gaze [(direct_CON + direct_INCON) > (averted_CON + averted_INCON)], increased signal was found in the right intraparietal sulcus (**Figure 5C**). The contrast of averted gaze vs direct gaze [(averted_CON + averted_INCON) > (direct_CON + direct_INCON)] did not show any suprathreshold activation. Similarly, significant clusters emerged in neither of the interactions of congruency and gaze [IA1: (direct_INCON > direct_CON) > (averted_INCON > averted_CON)] and [IA2: (averted_INCON > averted_CON) > (direct_INCON

> direct_CON)] (**Supplementary Table S3** for coordinates, T-values and cluster sizes).

In our psychophysiological interaction analysis, we analyzed how the right TPJ was coupled with the action network for the interactions of the experimental factors, i.e. IA1 and IA2 (**Supplementary Figure S2** and **Table S4** for coordinates, T-values and cluster sizes of all PPI contrasts). Statistical maps were thresholded at $P < 0.05$ (FWE) at voxel level. Results demonstrated that for IA1, which represented increased BOLD incongruency costs for direct compared to averted gaze, the right TPJ showed context-dependent connectivity with the IFG and the right middle temporal gyrus (**Figure 6**, brown color map). For IA2, reflecting increased BOLD incongruency costs for averted compared to direct gaze, activation in the seed region was coupled to activation in a dorsal network of superior and inferior parietal lobules, pre- and postcentral gyri, temporal gyri, occipital gyri, left superior, posterior medial, middle and IFG, right paracentral gyrus, left putamen and right cerebellum (**Figure 6**, blue/green color map).

Discussion

The present study investigated the effect of gaze perception on behavioral and neural correlates of action control of non-imitative re-actions. Our results demonstrate context-dependent functional integration of gaze and action control processes and our behavioral findings are in line with theories suggesting a relationship between gaze effects and autistic traits.

As hypothesized, we found a significantly lower percentage of correct responses and longer RTs when participants had to respond in a spatially incompatible manner to the VCs' gaze shifts (Iacoboni et al., 1996; Hietanen et al., 2006; Schilbach et al.,

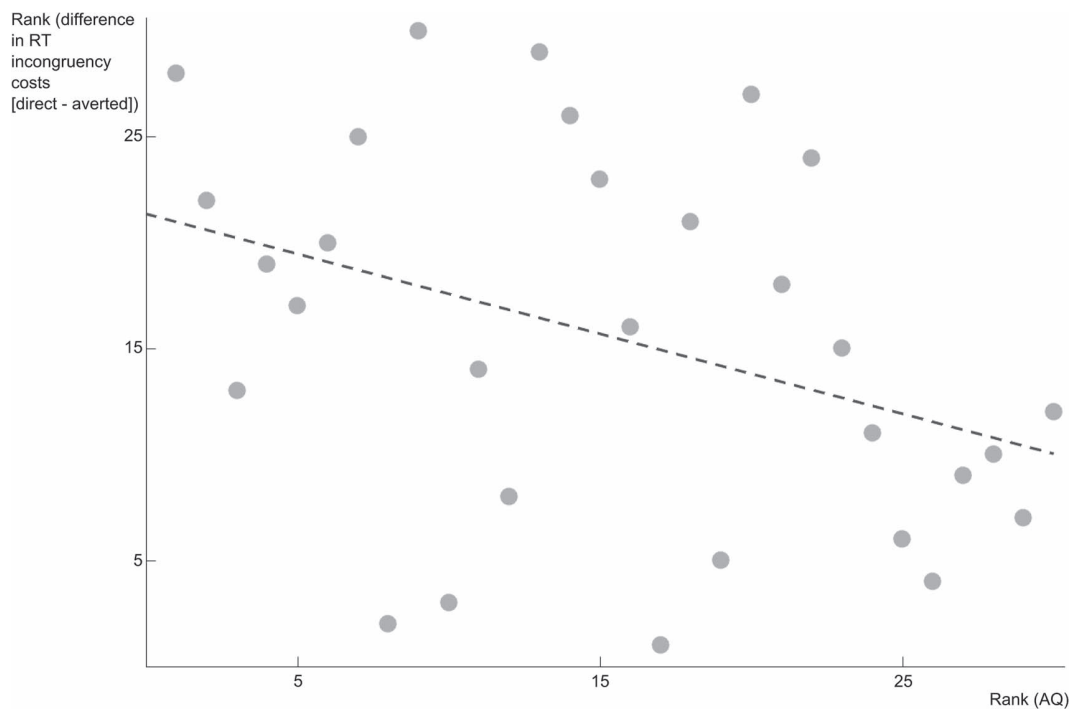


Fig. 4. Linear association of AQ scores and the difference in RT incongruency costs (ranks) between experimental conditions (direct—averted).

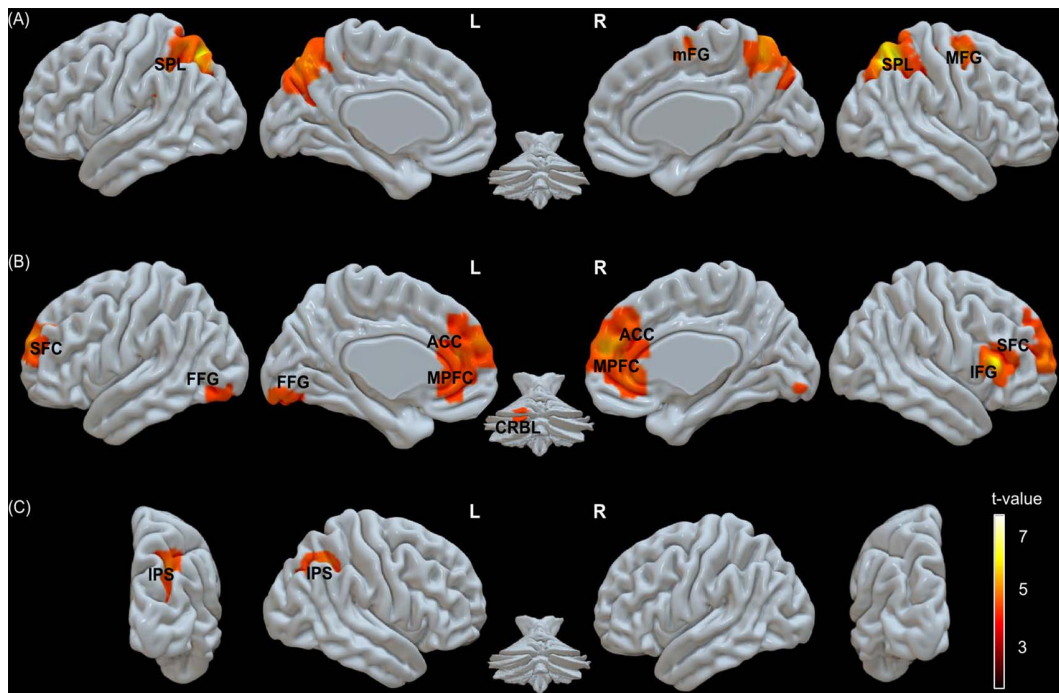


Fig. 5. Main effects of conditions in the left (L) and right (R) hemisphere. (A) Incongruent vs congruent, (B) congruent vs incongruent, (C) direct vs averted gaze. The cluster forming threshold was set to $P < 0.001$ (uncorrected), the cluster threshold to $P < 0.05$ (FWE) and cluster size (A) $k > 414$ voxels, (B) $k > 287$ voxels, (C) $k > 638$ voxels. [(A) SPL: superior parietal lobule, mFG: medial frontal gyrus; MFG: middle frontal gyrus (B) SFC: superior frontal cortex, FFG: fusiform gyrus, ACC: anterior cingulate cortex, MPFC: medial prefrontal cortex, CRBL: cerebellum; IFG: inferior frontal gyrus (C) IPS: intra-parietal sulcus].

2012). Moreover, in line with a priori expectations, key regions of the so-called dorsal fronto-parietal attention network showed increased activation in incongruent as compared to congruent experimental blocks, possibly reflecting the increased need for

top-down control (Corbetta and Shulman, 2002; Cieslik et al., 2015).

The opposite contrast, namely congruent vs incongruent, depicted increased brain activation in the left posterior fusiform

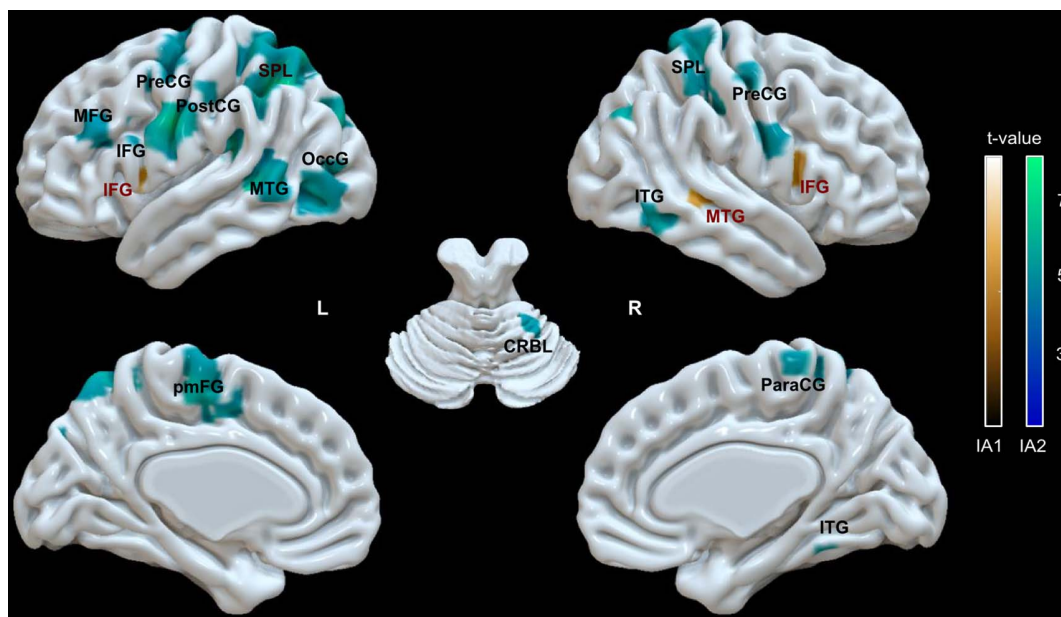


Fig. 6. Interaction effects in a psychophysiological interaction analysis in the left (L) and right (R) hemisphere. IA1 (brown): (direct_INCON > direct_CON) > (averted_INCON > averted_CON), IA2 (blue/green): (averted_INCON > averted_CON) > (direct_INCON > direct_CON). The results were FWE corrected at $P < 0.05$ voxel level. [IFG: inferior frontal gyrus, MTG: middle temporal gyrus MFG: middle frontal gyrus, PreCG: precentral gyrus, PostCG: postcentral gyrus, SPL: superior parietal lobule, OccG: occipital gyrus, CRBL: cerebellum, ITG: inferior temporal gyrus; pmFG: posterior medial frontal gyrus; ParaCG: paracentral gyrus].

gyrus and the MPFC. Given the lack of significant results in previous studies, we did not have specific hypotheses about the present contrast. A possible explanation for the brain activation found might be that similar to the sensitivity of the left fusiform gyrus towards faces and shapes (Kourtzi and Kanwisher, 2001), MPFC activation has previously been found in response to spatially congruent gaze shifts, potentially representing occurrences of joint attention (Bristow et al., 2007). Hence, in a situation of low task difficulty, participants might have used free cognitive capacities to thoroughly process the social encounter with a VC (Kanwisher et al., 1997). Alternatively, representing a central hub of the default mode network, which is known as the task-negative network (e.g. Fox et al., 2005), MPFC activation might indicate the occurrence of stimulus-independent thoughts that have been referred to as 'day dreaming' or mind wandering (Mason et al., 2007, Neurosynth, retrieved 3 June 2019: association of peak coordinates with terms 'default mode', 'mentalizing'). Despite of the richness of literature on the decisive role of the IFG in response inhibition processes (e.g. Zhang et al., 2017), in the present contrast, the right IFG was activated during congruent blocks not requiring to withdraw from or cancel motor actions. Instead, the IFG might have come into play through holding representations of the CV's gaze movements and hence, might have supported action understanding (Rizzolatti and Craighero, 2004; Casartelli and Molteni, 2014; Neurosynth, retrieved 3 June 2019: association of peak coordinates with terms 'decision task', 'comprehension', 'reappraisal'). Further, in light of its implication in gaze-grasping mappings (Bowman et al., 2009; Ambrosini et al., 2011), the IFG might have promoted a congruent button pressing by translating the gaze movement into a finger movement that corresponded to the direction of the gaze. Here, future research needs to clarify the specific role of the IFG during congruent task conditions.

Direct compared to averted gaze was followed by increased brain activation in the right intraparietal sulcus, a region known

to be involved in visuo-spatial aspects of action planning, the understanding of complex or irrational actions and the integration of visual and motor computations (Rizzolatti and Matelli, 2003; Fogassi and Luppino, 2005; Marsh and Hamilton, 2011). However, contrary to our hypotheses, direct gaze was not accompanied by increased activation in the right TPJ and fusiform gyrus—a result that might be caused by block design-induced habituation effects (Bruno et al., 2014).

Incongruity costs describe the behavioral or neural cost of performing a spatially incompatible motor response. In the present study, we were interested in the differences in incongruity costs between the direct and averted gaze conditions. Contrary to our hypothesis, incongruent RTs did not differ between the direct and the averted gaze condition. As has been shown previously (Wang et al., 2011a), in a more difficult task situation, gaze did not have an impact on behavior. However, contrary to the reported facilitation of motor imitation with direct gaze, in our study, the translation of a gaze shift into a left- or right-handed button press was less time-consuming for averted gaze movements. Thus, our results indicate that the facilitation effect of direct gaze might not apply to non-imitative behaviors. Consistent with behavioral results, there was no interaction effect of experimental conditions at the brain level.

The difference in RT incongruity costs between the direct and averted gaze condition represented a measure of the gaze-dependent incongruity effect on reaction speed. A correlation analysis showed that high AQ values were associated with higher incongruity costs in the averted gaze condition, whereas the difference in incongruity costs between conditions diminished and even changed towards higher incongruity costs in the direct gaze condition with decreasing AQ scores. This result points towards inter-individual differences in the sensitivity towards social gaze, as a function of autistic traits. In this sense, individuals with low AQ scores might be more susceptible to the influence of direct gaze than individuals with higher AQ values.

How the communication between the right TPJ and the action network changes depending upon the interplay of the experimental factors was addressed by means of a psychophysiological interaction analysis. Importantly, studies have indicated a functional partitioning of the right TPJ into an anterior and a posterior cluster: while the global functional integration of the anterior cluster suggests a mediating role in shifting from one functional brain state to another (Kernbach et al., 2018), our 'gaze'-associated seed region overlaps with the posterior TPJ cluster, implicated in social cognition, imagination and episodic memory retrieval (Bzdok et al., 2013). As hypothesized, the context-dependent connectivity between our seed and the IFG, known to be involved in the integration of action inhibitory tendencies and motivational, emotional or social input (e.g. Schulz et al., 2009; Chen et al., 2018; Neurosynth, retrieved 3 June 2019: association of peak coordinates with term 'theory of mind'), was increased for incongruity costs in the context of direct gaze. As a consequence, the connection between the right TPJ and the IFG might reflect an upregulated exchange of gaze information and inhibitory control processes in the context of direct gaze. Moreover, in parallel to the association of our TPJ region to object or scenic imagination (Bzdok et al., 2013), the IFG has been discussed not only to contribute to reactive but also proactive motor control (Aron, 2011; Di Russo et al., 2016). Accordingly, it would be possible that the IFG has been involved in preparing or anticipating a reorientation response that might have been supported by gaze-related input from the TPJ. In line with this post-hoc hypothesis, the right middle temporal gyrus has been indicated in mapping hypothetical motor actions to perceptual input (Hashimoto and Sakai, 2003).

Conversely, costs for reacting incongruently in the context of averted gaze as compared to direct gaze movements were represented in increased functional connectivity between our seed region and major parts of the action network, predominantly in the left hemisphere and including the parietal lobules, the primary motor and sensory cortex, the frontal and temporal gyri. Besides belonging to the action network, the superior parietal and frontal regions are also relevant in top down attentional control processes (Corbetta and Shulman, 2002; Vossel et al., 2012) and have been shown activated in working memory tasks, during spatial attention towards or the planning of actions (Ptak et al., 2017). In summary, incongruity costs for averted gaze appear to manifest in more wide-spread connectivity that encompasses somatosensory motor areas. Incongruity costs for direct gaze, however, are reflected in increased connectivity with brain regions that are involved in both action control and social cognition.

In conclusion, the results of the present study shed new light onto the neurobiology that underlies the specific role of direct gaze in social encounters: by increasing the connectivity of multimodal brain regions, the processing of direct gaze results in an integration of brain regions implicated in action control and social cognition. In this way, direct gaze could be seen as contributing to a comprehensive processing of the social situation that goes beyond a strongly stimulus-driven orientation.

Supplementary data

Supplementary data are available at SCAN online.

Funding

L.S. was supported by a grant for an Independent Max Planck Research Group by the Max Planck Society.

Conflict of interest. The authors declare no competing financial interests.

References

- Ambrosini, E., Costantini, M., Sinigaglia, C. (2011). Grasping with the eyes. *Journal of Neurophysiology*, **106**, 1437–42.
- Aron, A.R. (2011). From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. *Biological Psychiatry*, **69**, e55–68.
- Baron-Cohen, S., Wheelwright, S., Skinner, R., et al. (2001). The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders*, **31**, 5–17.
- Becchio, C., Bertone, C., Castiello, U. (2008). How the gaze of others influences object processing. *Trends in Cognitive Sciences*, **12**, 254–8.
- Böckler, A., van der Wel, R.P.R.D., Welsh, T.N. (2014). Catching eyes. *Psychological Science*, **25**, 720–7.
- Bowman, M.C., Johansson, R.S., Flanagan, J.R., et al. (2009). Eye-hand coordination in a sequential target contact task. *Experimental Brain Research*, **195**, 273–83.
- Brett, M., Anton, J., Valabregue, R., et al. (2002). Region of interest analysis using an SPM toolbox [abstract]. Presented at the 8th International Conference on Functional Mapping of the Human Brain, June 2-6, 2002, Sendai, Japan. Available on CD-ROM in NeuroImage, Vol 16, No 2.
- Bristow, D., Rees, G., Frith, C.D. (2007). Social interaction modifies neural response to gaze shifts. *Social Cognitive and Affective Neuroscience*, **2**, 52–61.
- Bruno, J.L., Garrett, A.S., Quintin, E.-M., et al. (2014). Aberrant face and gaze habituation in fragile X syndrome. *American Journal of Psychiatry*, **171**, 1099–106.
- Bzdok, D., Langner, R., Schilbach, L., et al. (2013). Characterization of the temporo-parietal junction by combining data-driven parcellation, complementary connectivity analyses, and functional decoding. *NeuroImage*, **81**, 381–92.
- Caballero-Gaudes, C., Reynolds, R.C. (2017). Methods for cleaning the BOLD fMRI signal. *NeuroImage*, **154**, 128–49.
- Calder, A.J., Lawrence, A.D., Keane, J., et al. (2002). Reading the mind from eye gaze. *Neuropsychologia*, **40**, 1129–38.
- Callejas, A., Shulman, G.L., Corbetta, M. (2014). Dorsal and ventral attention systems underlie social and symbolic cueing. *Journal of Cognitive Neuroscience*, **26**, 63–80.
- Casartelli, L., Molteni, M. (2014). Where there is a goal, there is a way: what, why and how the parieto-frontal mirror network can mediate imitative behaviours. *Neuroscience and Biobehavioral Reviews*, **47**, 177–93.
- Chen, T., Becker, B., Camilleri, J., et al. (2018). A domain-general brain network underlying emotional and cognitive interference processing: evidence from coordinate-based and functional connectivity meta-analyses. *Brain Structure and Function*, **223**, 3813–40.
- Cieslik, E.C., Mueller, V.I., Eickhoff, C.R., et al. (2015). Three key regions for supervisory attentional control: evidence from neuroimaging meta-analyses. *Neuroscience and Biobehavioral Reviews*, **48**, 22–34.
- Corbetta, M., Shulman, G.L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, **3**, 215–29.
- Di Russo, F., Lucci, G., Sulpizio, V., et al. (2016). Spatiotemporal brain mapping during preparation, perception, and action. *NeuroImage*, **126**, 1–14.

- Eickhoff, S.B., Stephan, K.E., Mohlberg, H., et al. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage*, **25**, 1325–35.
- Engell, A.D., Nummenmaa, L., Oosterhof, N.N., et al. (2010). Differential activation of frontoparietal attention networks by social and symbolic spatial cues. *Social Cognitive and Affective Neuroscience*, **5**, 432–40.
- Fogassi, L., Luppino, G. (2005). Motor functions of the parietal lobe. *Current Opinion in Neurobiology*, **15**, 626–31.
- Fox, M.D., Snyder, A.Z., Vincent, J.L., et al. (2005). From the cover: the human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences*, **102**, 9673–8.
- Friesen, C.K., Kingstone, A. (1998). The eyes have it! Reflexive orienting is triggered by nonpredictive gaze. *Psychonomic Bulletin and Review*, **5**, 490–5.
- Friston, K.J., Williams, S., Howard, R., et al. (1996). Movement-related effects in fMRI time-series. *Magnetic Resonance in Medicine*, **35**, 346–55.
- Hashimoto, Y., Sakai, K.L. (2003). Brain activations during conscious self-monitoring of speech production with delayed auditory feedback: an fMRI study. *Human Brain Mapping*, **20**, 22–8.
- Haxby, J.V., Hoffman, E.A., Gobbini, M.I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences*, **4**, 223–33.
- Hietanen, J.K., Nummenmaa, L., Nyman, M.J., et al. (2006). Automatic attention orienting by social and symbolic cues activates different neural networks: an fMRI study. *NeuroImage*, **33**, 406–13.
- Iacoboni, M., Woods, R.P., Mazziotta, J.C. (1996). Brain-behavior relationships: evidence from practice effects in spatial stimulus-response compatibility. *Journal of Neurophysiology*, **76**, 321–31.
- Kanwisher, N., McDermott, J., Chun, M.M. (1997). The fusiform face area: a module in human extrastriate cortex specialized for face perception. *Journal of Neuroscience*, **17**, 4302–11.
- Kernbach, J.M., Yeo, B.T.T., Smallwood, J., et al. (2018). Subspecialization within default mode nodes characterized in 10 000 UK Biobank participants. *Proceedings of the National Academy of Sciences of the United States of America*, **115**, 12295–300.
- Kiebel, S., Holmes, A. (2004). In: Frackowiak, K., Friston, K., Frith, C., et al., editors. *The general linear model, Human Brain Function 2*, London: Elsevier, pp. 725–60.
- Kourtzi, Z., Kanwisher, N. (2001). Representation of perceived object shape by the human lateral occipital complex. *Science*, **293**, 1506–9.
- Marsh, L.E., Hamilton, A.F.D.C. (2011). Dissociation of mirroring and mentalising systems in autism. *NeuroImage*, **56**, 1511–9.
- Mason, M.F., Norton, M.I., Van Horn, J.D., et al. (2007). Wandering minds: the default network and stimulus-independent thought. *Science*, **315**, 393–5.
- McLaren, D.G., Ries, M.L., Xu, G., et al. (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. *NeuroImage*, **61**, 1277–86.
- Nummenmaa, L., Passamonti, L., Rowe, J., et al. (2010). Connectivity analysis reveals a cortical network for eye gaze perception. *Cerebral Cortex (New York, N.Y.: 1991)*, **20**, 1780–7.
- Oldfield, R.C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *9*, 97–113.
- Pelphrey, K.A., Singerman, J.D., Allison, T., et al. (2003). Brain activation evoked by perception of gaze shifts: the influence of context. *Neuropsychologia*, **41**, 156–70.
- Pierno, A.C., Becchio, C., Wall, M.B., et al. (2006). When gaze turns into grasp. *Journal of Cognitive Neuroscience*, **18**, 2130–7.
- Prinsen, J., Bernaerts, S., Wang, Y., et al. (2017). Direct eye contact enhances mirroring of others' movements: a transcranial magnetic stimulation study. *Neuropsychologia*, **95**, 111–8.
- Ptak, R., Schneider, A., Fellrath, J. (2017). The dorsal frontoparietal network: a core system for emulated action. *Trends in Cognitive Sciences*, **21**, 589–99.
- Rizzolatti, G., Craighero, L. (2004). The mirror-neuron system. *Annual Review of Neuroscience*, **27**, 169–92.
- Rizzolatti, G., Matelli, M. (2003). Two different streams form the dorsal visual system: anatomy and functions. *Experimental Brain Research*, **153**, 146–57.
- Rorden, C., Brett, M. (2000). Stereotaxic display of brain lesions. *Behavioural Neurology*, **12**, 191–200.
- Schilbach, L., Eickhoff, S.B., Cieslik, E., et al. (2011). Eyes on me: an fMRI study of the effects of social gaze on action control. *Social Cognitive and Affective Neuroscience*, **6**, 393–403.
- Schilbach, L., Eickhoff, S.B., Cieslik, E.C., et al. (2012). Shall we do this together? Social gaze influences action control in a comparison group, but not in individuals with high-functioning autism. *Autism*, **16**, 151–62.
- Schilbach, L., Timmermans, B., Reddy, V., et al. (2013). Toward a second-person neuroscience. *Behavioral and Brain Sciences*, **36**, 393–414.
- Schobert, A.-K., Corradi-Dell'Acqua, C., Frühholz, S., et al. (2018). Functional organization of face processing in the human superior temporal sulcus: a 7T high-resolution fMRI study. *Social Cognitive and Affective Neuroscience*, **13**, 102–13.
- Schulz, K.P., Clerkin, S.M., Halperin, J.M., et al. (2009). Dissociable neural effects of stimulus valence and preceding context during the inhibition of responses to emotional faces. *Human Brain Mapping*, **30**, 2821–33.
- Schurz, M., Tholen, M.G., Perner, J., et al. (2017). Specifying the brain anatomy underlying temporo-parietal junction activations for theory of mind: a review using probabilistic atlases from different imaging modalities. *Human Brain Mapping*, **38**, 4788–805.
- Senju, A., Johnson, M.H. (2009). The eye contact effect: mechanisms and development. *Trends in Cognitive Sciences*, **13**, 127–34.
- Tanaka, J.W., Sung, A. (2016). The 'eye avoidance' hypothesis of autism face processing. *Journal of Autism and Developmental Disorders*, **46**, 1538–52.
- Vossel, S., Weidner, R., Driver, J., et al. (2012). Deconstructing the architecture of dorsal and ventral attention systems with dynamic causal modeling. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*, **32**, 10637–48.
- Wang, Y., Hamilton, A.F.D.C. (2012). Social top-down response modulation (STORM): a model of the control of mimicry in social interaction. *Frontiers in Human Neuroscience*, **6**, 153.
- Wang, Y., Newport, R., Hamilton, A.F.D.C. (2011a). Eye contact enhances mimicry of intransitive hand movements. *Biology Letters*, **7**, 7–10.
- Wang, Y., Ramsey, R., de C. Hamilton, A.F. (2011b). The control of mimicry by eye contact is mediated by medial prefrontal cortex. *Journal of Neuroscience*, **31**, 12001–10.
- Yarkoni, T., Poldrack, R.A., Nichols, T.E., et al. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods*, **8**, 665–70.
- Zhang, R., Geng, X., Lee, T.M.C. (2017). Large-scale functional neural network correlates of response inhibition: an fMRI meta-analysis. *Brain Structure and Function*, **222**, 3973–90.

4 Discussion

This thesis addressed the neural correlates of action signals within social interactions. In light of the interdependence of kinematics and social cognition (section 1.1) as well as the behavioral and brain abnormalities in these domains reported in ASD (sections 1.2, 1.3 & 1.4), this thesis aimed at deepening our understanding of the brain mechanisms behind the perception of social kinematic interactions and action control related to social signals. In this way, two modified experimental paradigms were tested in healthy control subjects to first, gain knowledge on non-pathological behavioral correlates and brain processes, second, establish two experimental fMRI paradigms that can be built on methodologically by providing brain loci of functional relevance and third, that can be taken as a reference for future studies on ASD.

4.1 The neural and behavioral correlates of IPPC

The first study of this thesis studied the phenomenon of IPPC (Zillekens, Brandi, et al., 2019). Considering the predictive nature of communicative as compared to individual actions, it has been shown that communicative actions automatically trigger inferences about intentions and enable the anticipation of complementary response actions (Becchio et al., 2012; Neri, Luu, & Levi, 2006). Autistic individuals, however, seem to be impaired in the perception and prediction of observed kinematic interactions (Pavlova, 2012; von der Lühne et al., 2016). Given this clinical significance, the first study targeted the BOLD correlates of IPPC in a group of healthy participants to gain knowledge on the brain mechanisms involved in making predictions from communicative actions.

4.1.1 Communicative signals shape visual perception

Within the noisy environmental conditions in our study, we hypothesized participants to emphasize prior information deduced from internal models about action intentions (Adams et al., 2015; Friston, 2002, 2005). In this way, the resulting perception of a second agent should be modulated by the type of kinematic signal. In line with this, participants were more successful in discriminating between the presence and absence of a second agent when the action of the first agent had been communicative (Zillekens, Brandi, et al., 2019).

Next, we analyzed possible effects of IPPC on the response criterion of participants, revealing the probability of perceiving a second agent or the bias towards positive

and negative responses, respectively (Stanislaw & Todorov, 1999). In our study, non-predictive individual actions led to a decreased probability of perceiving the second agent, i.e. a conservative response strategy, while communicative actions were accompanied by an unbiased response behavior (Zillekens, Brandi, et al., 2019). Answering the question of the predictive specificity of a communicative action, a previous study demonstrated that the effect of IPPC on the response criterion was specific for congruent actions of the second agent but disappeared when the response action did not match the communicative intention signaled by the first agent (Manera, Del Giudice, et al., 2011). This finding is important as it indicates that a communicative action does not signal the mere presence of a second agent but more specifically allows predicting the specific congruent action.

4.1.2 IPPC builds on social knowledge

The observation of individual as compared to communicative actions elicited increased BOLD signal in brain regions such as the pre- and postcentral motor cortices as well as superior parietal areas (Zillekens, Brandi, et al., 2019), which are recruited in order to execute cognitive control (Majerus et al., 2018; Vossel et al., 2012). Contrarily, when observing communicative vs. individual actions, increased BOLD signal was measured in the SFG, known to code for social knowledge (Koechlin et al., 2000; Wood et al., 2004). Thus, potentially by increasing the precision of perceptual evidence accumulation, IPPC seems to reduce executive control demands. These findings suggest that this prediction-driven perception might rely on higher-level cognitive models of event sequences that encourage prospective prediction making (Barbey, Krueger, & Grafman, 2009; Underwood, Guynn, & Cohen, 2015). Similar to guiding visual perception, scripts of event knowledge appear to affect fixation behavior and memory, prioritizing context-relevant over neutral items. Critically, this effect was only present in healthy control, but absent in high-functioning autistic children (Loth, Gómez, & Happé, 2011) who might not integrate predictions from higher-order models of event sequences into lower level sensory processes. In line with this, autistic participants do not profit from familiarity of presented event sequences when making predictions about the outcomes and their temporal alignment to observed goal-directed actions (Zalla, Labruyère, Clément, & Georgieff, 2010). This, again, implies inadequate neural representations of prior event knowledge in ASD, impeding experience transfer that subserves advantageous predictions, particularly in social interactions (Zalla, Labruyère, & Georgieff, 2006). Underlining the importance of the SFG, reduced recruitment and decreased functional connectivity of the SFG with temporal regions have been associated with ASD as compared to control participants during ToM tasks of moving geometric shapes (Kana, Keller, Cherkassky, Minshew, & Just, 2009). Based on these findings and its involvement in IPPC, we hypothesize the SFG to interact with brain regions implicated in mentalizing and in making experience-informed social event predictions.

4.1.3 The role of the amygdala in adapting to a predictive or non-predictive context

Task performance over conditions as measured by the sensitivity to discriminate between signal and noise negatively correlated with BOLD signal in the left amygdala (Zillekens, Brandi, et al., 2019). Besides emotional processing, the amygdala has also been implicated in attentional orienting, motivation, associative learning (Adolphs, 2010; Cardinal, Parkinson, Hall, & Everitt, 2002) as well as in the integration of stimulus-independent and stimulus-oriented processing (Bzdok, Laird, et al., 2013). In order to specify the role of the amygdala, we conducted a consecutive psychophysiological interaction analysis (Zillekens, Brandi, et al., 2019): While increased functional coupling with a fronto-parietal network occurred in an individual context, in the communicative condition, the amygdala worked in concert with the mPFC. The functional coupling with brain areas involved in task-related executive control and biological motion perception (Caspers, Zilles, Laird, & Eickhoff, 2010; Pavlova, 2012) suggest that the amygdala contributed by increasing attentional control to compensate for non-predictable stimuli and by shifting the focus to stimulus-driven perception. On the other hand, in a predictive context, amygdala activation was aligned with the mPFC as one of the key mentalizing regions of the brain (Amodio & Frith, 2006; Yang et al., 2015). This might reflect an automatic shift towards implicit social cognition (Satpute & Lieberman, 2006) evoked by communicative point-light agents. In Bayesian terms, individual actions required a stronger weighing of sensory input, prior predictions were to be assigned more weight for communicative actions. The implication of the amygdala thus might indicate difficulties in setting the optimal context-specific Bayesian mode. In comparison to the behavioral study, participants in the fMRI study adopted a more conservative response criterion in the communicative condition. Based on this observation, increased amygdala-mPFC coupling could also represent increased inhibitory control, particularly implemented by the anterior cingulate cortex, attenuating the effect of IPPC on perceptual sensitivity. Further, co-activity in the mPFC might display performance monitoring by integrating error or success feedback (Dehaene, Posner, & Tucker, 1994; Vidal, Hasbroucq, Grapperon, & Bonnet, 2000), which might have been translated into interfering emotional or motivational content.

Remarkably, autistic individuals have demonstrated increased variability in the functional integration of a ventral-temporal-limbic network enclosing the amygdala (Glerean et al., 2016). Similarly, decreased habituation to repeatedly shown social stimuli and findings of both hypo- and hyperactivity during face perception in the amygdala of autistic individuals have been interpreted as failure in flexibly adjusting brain processes to the demands of a social context (Dichter, 2012). Autistic individuals further demonstrated aberrant anatomical and functional connectivity of the amygdala (Gibbard, Ren, Skuse, Clayden, & Clark, 2018; Iidaka, Kogata, Mano, & Komeda, 2019; Pelphey et al., 2005). Yet, empirical findings are heterogeneous and might not take into consideration anatomical or behavioral phenomena such as reduced attentional focus, reduced fixation of social stimuli (Sato & Uono, 2019) or idiosyncratic brain activity during social perception (Hasson et al., 2009; Salmi et al., 2013). In order to elucidate the

unbiased role of the amygdala as crucial bastion in social cognition (Adolphs, 2010) in IPPC, the current paradigm (Zillekens, Brandi, et al., 2019) provides a framework that offers the analysis of online fixation behavior and that might further be augmented by structural brain measures.

4.1.4 Methodological considerations

The behavioral results of the first study of this thesis represent a replication of findings from previous studies using similar versions of the presented paradigm (Manera, Becchio, Schouten, et al., 2011; Okruszek et al., 2017; von der Lühe et al., 2016). Hence, IPPC seems to reliably act on human visual perception. Nevertheless, despite of the reliability of the effect, significant conditional differences from the behavioral study changed into insignificant trends in the fMRI study (Zillekens, Brandi, et al., 2019). As has been discussed in the paper, it needs to be taken into account that participants performed the pretest, which determined their individual level of difficulty in terms of the number of interfering dots, outside of the fMRI scanner. This discrepancy between the pretest and the test environment might have caused participants to respond more cautiously in the communicative condition and thus, to be less susceptible to IPPC. Support for this explanation comes from a triplet of studies showing a deteriorating effect of the scanner environment on motor reaction speed and attention (van Maanen, Forstmann, Keuken, Wagenmakers, & Heathcote, 2016). Interestingly, in our study, we observed a shift towards more conservative response patterns only in the communicative condition, which is in line with previously reported condition-dependent scanner effects (Hommel, Fischer, Colzato, van den Wildenberg, & Cellini, 2012). In our case, this could mean that IPPC is highly susceptible to the external environment. Based on this, at the cost of prolonging the time spend inside the fMRI scanner, it should be recommended keeping the pretest and test environment consistent, allowing participants to familiarize with both the task and the scanner characteristics.

A methodological advance of the first study of this thesis is the careful control of participants' gaze behavior (Zillekens, Brandi, et al., 2019). By tracking the fixation pattern and gaze movements during each trial, we were able to discard those trials in which participant did not follow task instructions, i.e. did not fixate the first and the second agent. In this way, we ensured that participants experienced the experimental manipulation of seeing a communicative or an individual action.

4.2 Gaze processing and action control

The second study of this thesis investigated the interaction of gaze processing and action control (Zillekens, Schliephake, et al., 2019). More specifically, the study addressed the empirical gap of BOLD correlates of the interplay between direct gaze signals and complementary action control demands. In this way, two strains of the core clinical

symptomatology in ASD were connected: On the one hand, abnormal behavioral and neural responses to gaze have been related to the mindblindness in ASD (Baron-Cohen, 1995). On the other hand, motor control deficits represent core autistic characteristics (subsection 1.4.3). Importantly, while the integration of gaze information into action planning has been described as automatic and essential process within social interactions, actions of autistic individuals seem to be unaffected by direct gaze signals (Becchio et al., 2007; Schilbach et al., 2012).

4.2.1 The direct gaze effect and autistic traits

In order to find out whether the autistic insensitivity to the direct gaze effect transfers to the non-pathological range, we measured the manifestations of autistic traits in our group of healthy participants (Zillekens, Schliephake, et al., 2019). In extension of previous results attributing autistic traits to decreased proactive inhibitory control in a non-social context (Amoruso et al., 2018), we found that autistic traits were associated with the differential impact of direct gaze on high vs. low action control demands (Zillekens, Schliephake, et al., 2019). Suggesting a relationship between autistic traits and interconnectedness of direct gaze and motor control even in the non-pathological range of the autistic spectrum, this result underlines the need for further clinical research on action control processes within a social context.

4.2.2 Incongruency costs reflected in connectivity of the right TPJ

In light of abnormalities in gaze behavior and processing as well as atypical TPJ reactivity and functional connectedness in ASD (section 1.4), the focus of the second study rested on the context-dependent connectivity of the right TPJ as our hub gaze processing region with an action network (Zillekens, Schliephake, et al., 2019). To elucidate the differential connectivity profile of the right TPJ in dependence on gaze and action control demands, we conducted a psychophysiological interaction analysis and contrasted incongruency costs for direct and averted gaze. This means that we identified the gaze-specific costs for spatially incompatible responses in terms of functional connectivity of the right TPJ. Results demonstrate that incongruency costs for spatially incompatible responses to averted gaze shifts are expressed in increased connectivity of the right TPJ with widespread action control areas, involving somatosensory and motor regions. Thus, in line with literature on action control in non-social settings, the TPJ increased functional connectivity with areas implicated in top-down attentional control when confronted with increased action control effort in response to averted gaze (Corbetta & Shulman, 2002; Vossel et al., 2012). Conversely, increased functional coupling of our seed region with the inferior frontal gyrus and the middle temporal gyrus depicted incongruency costs for incongruent responses to direct gaze movements (Figure 7). This means that the context of direct gaze exhibited increased communication between our gaze processing hub and brain regions supporting not only reactive action inhibition, but also proactive motor

projections (Aron, 2011; Di Russo et al., 2016; Hashimoto & Sakai, 2003). Moreover, the inferior frontal gyrus has also been related to social cognition, merging action goals and social content such as emotional or motivational aspects (Chen et al., 2018; Schulz et al., 2009). As a conclusion, in a communicative context, the right TPJ might have mediated between gaze processing and action control as crucial elements of social interactions.

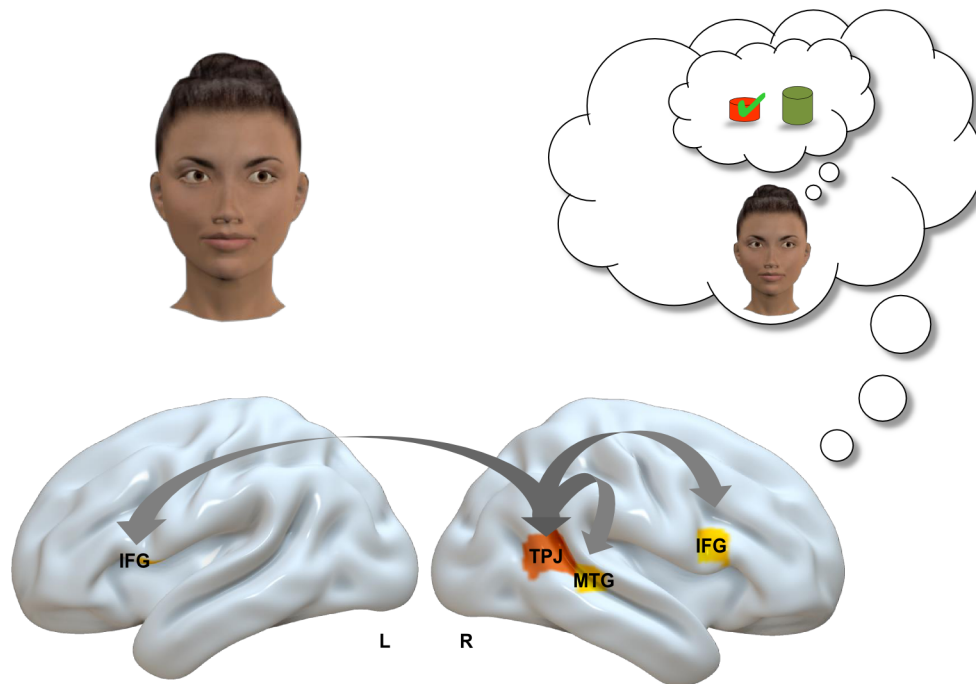


Figure 7. Context-dependent functional integration of the right TPJ. The right TPJ shows increased functional coupling with the left and right inferior frontal gyrus (IFG) as well as the right middle temporal gyrus (MTG) in a context of direct gaze and high action control demands, indicating an integration of gaze information, social cognition and action control processes. [Virtual character created in Poser 10 (Smith Micro Software, Inc., CA, USA) by L. M. Schliephake; brain image created in Surf Ice (Neuroimaging Informatics Tools and Resources Clearinghouse, retrieved from <https://www.nitrc.org/projects/surface/>)]

4.2.3 The role of the follower and implicit mentalizing

The simulated encounter with the virtual character did not resemble a reciprocal interaction as the virtual character did not react to the behavior of the participant (Zillekens, Schliephake, et al., 2019). Instead, we created a unidirectional interaction, assigning the role of the follower to participants. Here, taking into account role-specific brain correlates, BOLD signal in leaders seems to reflect self-centered cognition while studies have revealed that followers more strongly recruit brain regions such as the TPJ or the posterior cingulate cortex, which have been implicated in intention-related mentalizing (Atique, Erb, Gharabaghi, Grodd, & Anders, 2011; Chauvigné & Brown, 2018; Fairhurst, Janata, & Keller, 2014). As a consequence, the presented paradigm is deemed to be well suited in studying implicit ToM.

4.2.4 Action control beyond imitation and beyond social cues

Diverging from a large body of research on imitative control in a social context (e.g. L. E. Marsh & Hamilton, 2011; Wang et al., 2011), the second study of this thesis (Zillekens, Schliephake, et al., 2019) sheds light on the BOLD correlates of complementary actions, reflecting the building blocks of a reciprocal social interaction (Sartori & Betti, 2015). Another strength is the implementation of averted gaze as compared to non-social stimuli in the control condition. In this way, the experimental paradigm was a sensitive approach to the specific effect of direct gaze on action control. Furthermore, we analyzed action control of motor reactions that directly followed the gaze movements of the virtual character. This approach considered the significance of direct gaze as a communicative signal (Senju & Johnson, 2009a) which, we suggest, represented an ecologically more valid scenario than treating gaze or faces as background stimuli. Moreover, by requesting a direct response to gaze shifts, the focus was moved from attentional effects of direct gaze as a cue (e.g. Engell et al., 2010; Joseph et al., 2015) to the direct linkage of gaze shift and action execution (Zillekens, Schliephake, et al., 2019).

4.2.5 Experimental design and potential modifications

In the second study of this thesis, both gaze and spatial congruency were implemented as blocked experimental factors (Zillekens, Schliephake, et al., 2019). Within each block, gaze shifts occurred at an unpredictable pace. In this way, our design profited from the statistical power of blocked and stochastic designs in detecting fMRI BOLD and connectivity effects (Birn, Cox, & Bandettini, 2002; Cisler, Bush, & Steele, 2014; Friston et al., 1998). Furthermore, we modeled blocked gaze shifts as epochs, thereby taking into account the continuous exposure to the virtual character demonstrating direct or averted gaze (Zillekens, Schliephake, et al., 2019). Despite the aforementioned advantages, a disadvantage of block designs concerns the inflexible exclusion of single erroneous trials from the blocks (Chee, Venkatraman, Westphal, & Siong, 2003). For this reason, we selected a conservative boundary of nine out of 12 trials, which were required to be correct in order for a block to be included in our analysis (Zillekens, Schliephake, et al., 2019).

The experimental design raises another point of discussion: While the timing of gaze shifts was unpredictable, participants could familiarize with the type of gaze displayed as well as the congruency of the requested reactions (Zillekens, Schliephake, et al., 2019). This might have caused habituation effects, leading to an attenuation of the BOLD response over the course of the block (Breiter et al., 1996; Buckner, 1998; Fischer, Furmark, Wik, & Fredrikson, 2000). In order to circumvent habituation to the gaze stimulus, an alternative approach in future studies would be to implement direct and indirect gaze as rapid events within the different blocks of congruency. Another prospect of this procedure is that erroneous trials would be removable by modelling single events as stick functions (Mechelli, Henson, Price, & Friston, 2003). Parametric modulators such

as trial-wise pupil dilation or reaction times might additionally be used to correct for or investigate psychophysiology-specific BOLD effects (Büchel, Holmes, Rees, & Friston, 1998).

4.3 General discussion and outlook

The two studies presented in this thesis offer two distinct approaches to kinematics in a social context. While the first study addressed the perception of social actions from a third-person perspective (Zillekens, Brandi, et al., 2019), the second study investigated action control in response to social gaze signals from a second-person perspective (Zillekens, Schliephake, et al., 2019). In this way, both studies aimed at gaining knowledge on key aspects of social kinematics that have been shown to be impaired in ASD. In light of the lack of evidence on the brain processes related to action signals in social interactions, two experimental paradigms that are known to elicit atypical behavioral responses in autistic individuals were refined as fMRI experiments to identify the brain structures relevant in the integration of social cognition and kinematic processing.

4.3.1 fMRI: valuable approach despite methodological limitations

By the use of fMRI, we were able to non-invasively identify brain regions associated with the phenomena of interest at a high spatial resolution and in cortical as well as subcortical regions (Logothetis, 2002). Yet, at the same time as looking at the methodological opportunities, the limitations of fMRI need to be considered: First, fMRI does not directly measure neural activity (Raichle, 2009). Instead, the BOLD signal reflects task-evoked changes in the magnetic resonance from hydrogen ions in the blood vessels adjacent to the grey matter of the brain. Being accompanied by metabolic reactions, neural activity of an ensemble of neurons co-occurs with changes in the proportion of (de-)oxygenated hemoglobin in the blood. While oxygenated hemoglobin behaves diamagnetically, the oxygen-free iron ions on deoxygenated hemoglobin causes the molecule to be paramagnetic. Thus, the presence of deoxygenated hemoglobin interferes with the magnetic field induced by an fMRI scanner, which accelerates dephasing of previously aligned hydrogen ions, attenuating the BOLD signal resonance measured (Logothetis, 2008). Notably, it has been argued that signal changes do not permit to draw conclusions about neural inhibitions vs. excitation or to directly compare the magnitude of the BOLD response between brain regions, as the signal depends on local anatomical constraints and the size of the activated neuronal population (Logothetis, 2008). Second, the minimal temporal delay between MR pulses [repetition time (TR)] and the stimulus-evoked BOLD response determine the temporal resolution of the method. The latter is assumed to follow a particular course of approximately 20-30 seconds until reaching its initial baseline level, which can be modeled by the so-called *hemodynamic response function* (Logothetis, 2002; Taylor, Kim, & Rees, 2018).

Keeping the limitations of the method in mind, fMRI nevertheless constitutes a powerful tool to infer associations between brain region and function or behavior, indicating functional segregation or integration (Friston, 2009). Further, after functionally characterizing brain regions, we can now overcome the temporal boundaries of fMRI by conducting hypothesis-driven electroencephalography (EEG) or magnetoencephalography (MEG) studies that allow capturing millisecond changes in electrical or electromagnetic field potentials, respectively (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). Based on this rationale, a subsequent EEG study has been conducted that focusses on the brain loci identified in the first study of this thesis (Zillekens, Brandi, et al., 2019) to investigate the temporal dynamics of IPPC (Friedrich, Zillekens, Biel, Sauseng, and Schilbach, in prep.). Based on studies showing that correct predictions are associated with increased delta-band locking in higher-order cognitive regions whereas prediction errors are manifested in electrical gamma and beta locking in primary sensory areas (Arnal, Wyart, & Giraud, 2011; Friston, 2005), high- and low-frequency locking should be discriminative between communicative actions followed by a second agent and communicative actions followed by noise. Furthermore, low-frequency activity in the SFG, conceptualizing abstract social event sequences, should be measurable when observing communicative actions. In autistic individuals, the investigation of IPPC in an EEG design would allow to investigate whether error signals are generated and whether they inform higher-order conceptual models (Arnal et al., 2011; Friston, 2005).

In line with general recommendations, the two studies of this thesis did not exclusively study BOLD signal, but enriched the design through behavioral and psychological outcome measures, namely sensitivity, reaction times and AQ scores (Logothetis, 2008). Future studies might put more emphasis on physiological parameters like heart rate variability, pupil dilations or skin conductance, representing key sympathetic readouts that potentially account for inter-individual variance in an autistic sample (Cohen, Masyn, Mastergeorge, & Hessel, 2015; Klusek, Martin, & Losh, 2013) and might also be used as parametric modulators (Büchel et al., 1998).

As has been done for the amygdala seed in the first study of this thesis (Zillekens, Brandi, et al., 2019), the ROI in the right TPJ and the action brain mask from the second study (Zillekens, Schliephake, et al., 2019) were derived from meta-analytic association masks in Neurosynth of the terms “gaze” and “action” (Yarkoni et al., 2011). This means that ROI and brain map coordinates were corroborated by a critical assessment of the subject-specific body of existing literature (Poldrack, 2011). Statistically speaking, the selected ROIs consistently showed an association with the target terms, e.g. “gaze”, thereby increasing the generalizability of our results (Button et al., 2013).

4.3.2 From a third- to a second-person perspective

The two studies presented here complement each other in a two-fold manner: First, the kinematic content evolved from rather abstract and complex action perception and pre-

diction to hands-on action execution and control. Second, the interactive involvement of the participants was modulated by moving from a third- to a second-person perspective. As a conjunction, the two studies of this thesis attempted to investigate social kinematics from two different angles of abstraction and personal involvement. Still, studying behavioral and BOLD outcome measures in one individual in isolation does not consider interactive dynamics of real world interactions. Hence, researchers put forward the need for a *simultaneous dual-brain approach*, allowing for bidirectional interactions as well as the analysis of inter-brain connectivity as a measure of interactive brain function (Hari & Kujala, 2009; Redcay & Schilbach, 2019). However, turning the coin, the dual-brain approach comes at the cost of complexity and a trade-off between the degree of “true” interactiveness, and the degrees of freedom in the interaction or the ecological validity of the interactive situation. In the presented approach, at the loss of contingent reciprocity, it was possible to work with a complex but highly controllable stimulus material, displaying social event sequences and gaze movements of a virtual character.

Another starting point towards a simultaneous dual-brain approach might be to use knowledge we have gained on the structure and function of individuals with disorders of social interaction to simulate brain dynamics between interaction partners. As an example, the *dynamic Kuramoto model* (Kuramoto, 1975) has successfully been used to simulate functional intra- and inter-brain connectivity based on anatomical constraints (Breakspear, Heitmann, & Daffertshofer, 2010; Dumas, Chavez, Nadel, & Martinerie, 2012; Lee & Frangou, 2017). By forming simulated dyads of two autistic, two non-autistic individuals and an autistic and a non-autistic individual, the functional coupling of regions such as the SFG, the amygdala or the right TPJ can be analyzed across virtually interacting brains (Dumas et al., in prep.). Besides potentially solidifying empirical evidence of the importance of the respective structures in social interactions, a simulation approach further offers to predict the effects of external system modifications, for instance induced by brain stimulation. Moreover, concrete hypotheses derived from a simulation study and anatomical targets identified by fMRI might facilitate real dual brain approaches by the use of technologies such as EEG or functional near-infrared spectroscopy (fNIRS) that, compared to fMRI, offer increased kinematic freedom and therefore more realistic interactive designs (e.g. Dumas, Nadel, Soussignan, Martinerie, & Garnero, 2010).

4.3.3 Towards a psycho-behavioral BOLD endophenotype

In the case of ASD, biomarkers are yet unavailable and diagnoses are still based on behavioral observations instead of objective and biologically grounded diagnostic tests (Kapur, Phillips, & Insel, 2012). Particularly in the high-functioning spectrum of the disorder, individuals who might have developed coping strategies in order to deal with the challenges of the social environment are difficult to diagnose (Haker, Schneebeli, & Stephan, 2016). The lack of testable biomarkers thus inherits the risk of missing cases and the current diagnostic gold standards, i.e. an extensive experience-dependent diagnostic procedure, might further impede exhaustive screening and might delay diagnostic classifications

that entail adequate treatment or support (Lai et al., 2014). As they are often the reason for seeking clinical help, comorbid disorders such as major depressive disorder, social anxiety disorder or attention deficit hyperactivity disorder are often predominantly treated instead of ASD, which might remain undiagnosed (James, Mukaetova-Ladinska, Reichelt, Briel, & Scully, 2006; van Niekerk et al., 2011). Overall, the diagnostic category “ASD” embraces a wide pool of symptom expressions, comorbidities and developmental trajectories. In light of this heterogeneity, taxonomic subtyping or stratification from biomarkers or psychophysiological endophenotypes might be a promising avenue towards more tailored and successful interventions (Lai et al., 2014; Trusheim, Berndt, & Douglas, 2007). Crucially, neurocognitive and psychological measures collected by means of the two paradigms of this thesis might represent informative endophenotypes (Figure 8) that could be used to inform the clinician about the most suitable intervention strategy (Kapur et al., 2012). Although both studies of this thesis were conducted on healthy control participants, behavioral correlates in the second study of this thesis were related to autistic traits and the analyses of context-dependent functional connectivity in both studies focused on brain areas of fundamental importance in ASD. In the first study, the amygdala embodied the region of interest in our psychophysiological interaction analysis (Zillekens, Brandi, et al., 2019), in the second study, the TPJ was chosen as ROI (Zillekens, Schliephake, et al., 2019). As has been described earlier (subsections 4.1.3 & 1.4.2), ASD has been associated with abnormal BOLD activation and functional connectivity of the amygdala and the gaze-sensitive TPJ. Given these numerous ROI-related implications in ASD as well as the relevance of the respective brain structures in IPPC and gaze-dependent action control, the two studies of this thesis potentially addressed condition-relevant BOLD endophenotypes in ASD.

Besides broadening our understanding of the psychiatric condition, future studies in ASD patients should test whether these endophenotypes might be predictive of treatment outcome. For instance, in order to predict the probability of success of TPJ brain stimulation, medication or social trainings, model-based analyses on the one and machine learning on the other hand are evolving as promising approaches towards individualized treatment in psychiatry: Model-based analyses, for example within a Bayesian framework, might both be fruitful in explaining the symptomatology in ASD and also in informing diagnostic tests that output individualized model parameters of priors, prediction errors and precision weights (Haker et al., 2016). The hope would be that the model parameters of autistic individuals cluster into homogeneous subtypes of shared biological mechanisms, which the treatment could be adjusted to. Machine learning, also referred to as artificial intelligence, in turn, represents a form of *algorithmic modeling* and does not rely on theoretically grounded models of the disorder of interest. That is, as opposed to traditional inferential statistics, machine learning algorithms are independent of stochastic model assumptions about the underlying data (Breiman, 2001). In this way, while not providing a mechanistic disease model or probabilistic distribution of a clinical population, machine learning algorithms have already proven valuable in diagnostics and the prediction of individual health trajectories or treatment outcomes

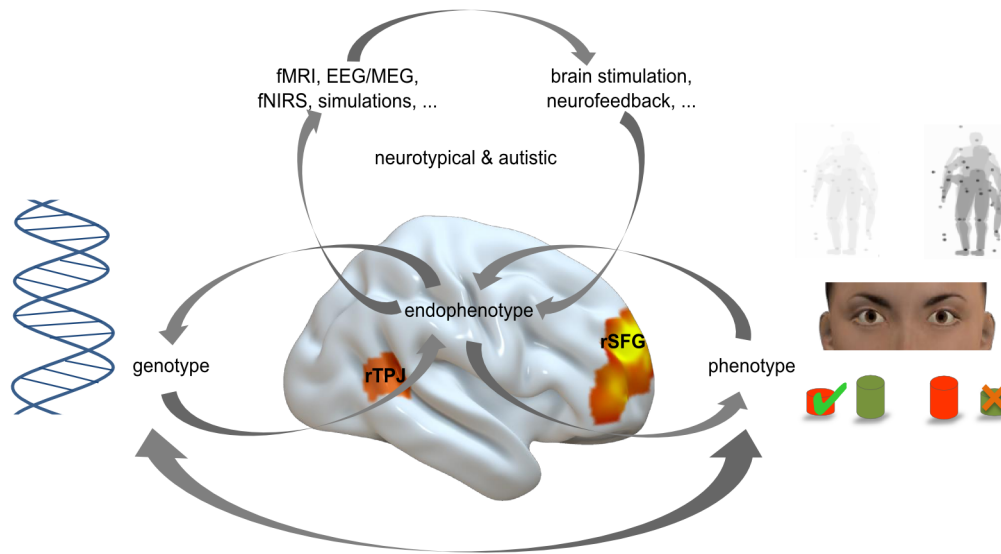


Figure 8. *BOLD correlates of the two studies in this thesis as potential endophenotypes in ASD.* Activity in the right SFG and the functional integration in the right TPJ have been related to behavioral phenotypes associated with ASD. Results can inform future studies and intervention programs to modulate the autistic phenotypes. [Brain image created in Surf Ice (Neuroimaging Informatics Tools and Resources Clearinghouse, retrieved from <https://www.nitrc.org/projects/surface/>); original point-light figure published in Manera, Becchio, Schouten, et al. (2011)]; virtual character created in Poser 10 (Smith Micro Software, Inc., CA, USA) by L. M. Schliephake]

(Dwyer, Falkai, & Koutsouleris, 2018; Topol, 2019). As such, they have the potential to augment a clinician's basis of decision-making in psychiatric conditions such as ASD.

4.3.4 Interventions

Non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS) can be used to modulate brain activation in cortical regions, thereby interfering with functional network dynamics. Research in this field has shown that excitatory brain stimulation on the right TPJ via anodal tDCS can enhance the performance in tasks that require perspective taking, ToM or imitative action control (Santesteban, Banissy, Catmur, & Bird, 2012, 2015; Sowden, Wright, Banissy, Catmur, & Bird, 2015). Moreover, compared to the stimulation of the central electrode scalp location as indexed by the 1020 electrodes EEG system, online trains of TMS pulses on the right TPJ leads to a reduced integration of event predictions into action commands (Bardi, Six, & Brass, 2017). Thus, evidence suggests that both social cognition and action control might be subject to changes induced by brain stimulation. Following on these lines, tDCS and TMS are promising methods to enhance or interfere with the integration of social and motor computations. Additionally considering the integral role of the TPJ in biological motion perception (Giese & Poggio, 2003), brain stimulation of the right TPJ might also promote IPPC. Equivalently, the SFG might embody

a target region for brain stimulation to facilitate access to and to develop generalizable internal models of stimulus-event sequences (subsection 4.1.2).

Neurofeedback-supported training interventions resemble another promising approach to enable autistic individuals to modulate their cognitive responses to socially relevant stimuli (Carelli et al., 2017; Friedrich et al., 2014). For instance, Ramot et al. (2017) have used real-time fMRI neurofeedback to train autistic participants to regulate functional connectivity between the superior temporal sulcus and somatosensory regions. Persisting network changes evolved that were correlated with behavioral changes in “social responsiveness”. Similar results after neurofeedback training have been reported in motor control areas, corresponding to changes in symptom severity of social interactive impairments (Datko, Pineda, & Müller, 2018). In combination with neurofeedback, the stimulus material presented in this thesis could be used to help participants to specifically train network dynamics relevant in action processing and social cognition.

4.4 Conclusions

Overall, the paradigms of this thesis represent powerful tools for investigating kinematic elements of social interactions (Zillekens, Brandi, et al., 2019; Zillekens, Schliephake, et al., 2019). Specifically, this thesis investigated the neurotypical BOLD correlates of the perception and the execution of actions within social interactions, highlighting the roles of the SFG, the amygdala as well as the right TPJ in adjusting neural processing and network dynamics to meet the demands of the socio-motor context. As a conclusion, this thesis addresses fundamental processes of social interactions, increases our knowledge on the neural mechanisms involved and links results to the expression of autistic traits. The findings further form the first cornerstones following studies can build on to investigate the temporal dynamics of IPPC (Friedrich et al., in prep.), inter-brain connectivity (Dumas et al., in prep.) and their disruption in autistic individuals. By means of machine learning and model-based analyses, future studies should aim at connecting the behavioral, psychological and neurological endophenotypes with treatment outcomes related to therapeutic and medical interventions as well as brain stimulation or neurofeedback protocols – to serve the goal of translating research on ASD into individualized, early intervention.

Bibliography

- Adams, R. A., Brown, H. R., & Friston, K. J. (2015). *Bayesian inference, predictive coding and delusions*.
- Adolphs, R. (2009). The social brain: neural basis of social knowledge. *Annual review of psychology, 60*, 693–716.
- Adolphs, R. (2010). What does the amygdala contribute to social cognition? *Annals of the New York Academy of Sciences, 1191*(1), 42–61.
- Aglioti, S. M., Cesari, P., Romani, M., & Urgesi, C. (2008). Action anticipation and motor resonance in elite basketball players. *Nature Neuroscience, 11*(9), 1109–1116.
- Albantakis, L., Parpart, H., Krankenhagen, M., Böhm, J., Henco, L., Brandi, M., & Schilbach, L. (2018). The Munich Autism Cohort: Clinical characterization of adult individuals with high-functioning autism from a clinic for disorders of social interaction. *Persönlichkeitsstörungen: Theorie und Therapie, 56*–61.
- Albantakis, L., Parpart, H., Thaler, H., Krankenhagen, M., Böhm, J., Zillekens, I. C., & Schilbach, L. (2018). Depression bei Erwachsenen mit Autismus-Spektrum-Störung. *Nervenheilkunde*.
- Alkire, D., Levitas, D., Warnell, K. R., & Redcay, E. (2018). Social interaction recruits mentalizing and reward systems in middle childhood. *Human Brain Mapping, 39*(10), 3928–3942.
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA.
- Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: the medial frontal cortex and social cognition. *Nature Reviews Neuroscience, 7*(4), 268–277.
- Amoruso, L., Finisguerra, A., & Urgesi, C. (2018). Autistic traits predict poor integration between top-down contextual expectations and movement kinematics during action observation. *Scientific Reports, 8*(1), 16208.
- Arnal, L. H., Wyart, V., & Giraud, A.-L. (2011). Transitions in neural oscillations reflect prediction errors generated in audiovisual speech. *Nature Neuroscience, 14*(6), 797–801.
- Aron, A. R. (2011). From Reactive to Proactive and Selective Control: Developing a Richer Model for Stopping Inappropriate Responses. *Biological Psychiatry, 69*(12), e55–e68.
- Asperger, H. (1944). Die Autistischen Psychopathen im Kindesalter. *Archiv für Psychiatrie und Nervenkrankheiten, 117*(1), 76–136.
- Atique, B., Erb, M., Gharabaghi, A., Grodd, W., & Anders, S. (2011). Task-specific activity and connectivity within the mentalizing network during emotion and intention mentalizing. *NeuroImage, 55*(4), 1899–1911.
- Bailenson, J. N., & Yee, N. (2005). Digital Chameleons: Automatic Assimilation of Nonverbal Gestures in Immersive Virtual Environments. *Psychological Science, 16*(10), 814–819.
- Barbey, A. K., Krueger, F., & Grafman, J. (2009). Structured event complexes in the medial prefrontal cortex support counterfactual representations for future planning. *Philosophical Transactions of the Royal Society B: Biological Sciences, 364*(1521), 1291–1300.
- Bardi, L., Six, P., & Brass, M. (2017). Repetitive TMS of the temporo-parietal junction disrupts participant's expectations in a spontaneous Theory of Mind task. *Social cognitive and affective neuroscience, 12*(11), 1775–1782.

BIBLIOGRAPHY

- Baron-Cohen, S. (1995). *Mindblindness: An Essay on Autism and Theory of Mind*. Cambridge, MA: MIT Press.
- Baron-Cohen, S., Jolliffe, T., Mortimore, C., & Robertson, M. (1997). Another advanced test of theory of mind: evidence from very high functioning adults with autism or asperger syndrome. *Journal of child psychology and psychiatry, and allied disciplines*, 38(7), 813–22.
- Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *Journal of child psychology and psychiatry, and allied disciplines*, 42(2), 241–51.
- Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of autism and developmental disorders*, 31(1), 5–17.
- Beauchaine, T. P., & Constantino, J. N. (2017). Redefining the endophenotype concept to accommodate transdiagnostic vulnerabilities and etiological complexity. *Biomarkers in medicine*, 11(9), 769–780.
- Becchio, C., Bertone, C., & Castiello, U. (2008). How the gaze of others influences object processing. *Trends in Cognitive Sciences*, 12(7), 254–258.
- Becchio, C., Manera, V., Sartori, L., Cavallo, A., & Castiello, U. (2012). Grasping intentions: from thought experiments to empirical evidence. *Frontiers in human neuroscience*, 6, 117.
- Becchio, C., Pierno, A., Mari, M., Lusher, D., & Castiello, U. (2007). Motor contagion from gaze: the case of autism. *Brain*, 130(9), 2401–2411.
- Becchio, C., Sartori, L., Bulgheroni, M., & Castiello, U. (2008). The case of Dr. Jekyll and Mr. Hyde: A kinematic study on social intention. *Consciousness and Cognition*, 17(3), 557–564.
- Becchio, C., Sartori, L., & Castiello, U. (2010). Toward You. *Current Directions in Psychological Science*, 19(3), 183–188.
- Birn, R. M., Cox, R. W., & Bandettini, P. A. (2002). Detection versus Estimation in Event-Related fMRI: Choosing the Optimal Stimulus Timing. *NeuroImage*, 15(1), 252–264.
- Bishop-Fitzpatrick, L., Mazefsky, C. A., Minshew, N. J., & Eack, S. M. (2015). The relationship between stress and social functioning in adults with autism spectrum disorder and without intellectual disability. *Autism research : official journal of the International Society for Autism Research*, 8(2), 164–73.
- Blakemore, S.-J., & Decety, J. (2001). From the perception of action to the understanding of intention. *Nature Reviews Neuroscience*, 2(8), 561–567.
- Blank, H., & Davis, M. H. (2016). Prediction Errors but Not Sharpened Signals Simulate Multivoxel fMRI Patterns during Speech Perception. *PLOS Biology*, 14(11), e1002577.
- Blaxill, M. F. (2004). What's Going on? The Question of Time Trends in Autism. *Public Health Reports*, 119(6), 536–551.
- Böckler, A., van der Wel, R. P. R. D., & Welsh, T. N. (2014). Catching Eyes. *Psychological Science*, 25(3), 720–727.
- Bowler, D. M. (1992). Theory of Mind in Asperger's Syndrome Dermot M. Bowler. *Journal of Child Psychology and Psychiatry*, 33(5), 877–893.
- Brass, M., Ruby, P., & Spengler, S. (2009). Inhibition of imitative behaviour and social cognition. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 364(1528), 2359–67.
- Breakspear, M., Heitmann, S., & Daffertshofer, A. (2010). Generative Models of Cortical Oscillations: Neurobiological Implications of the Kuramoto Model. *Frontiers in Human Neuroscience*, 4, 190.

- Breiman, L. (2001). Statistical Modeling: The Two Cultures (with comments and a rejoinder by the author). *Statistical Science*, 16(3), 199–231.
- Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., ... Rosen, B. R. (1996). Response and Habituation of the Human Amygdala during Visual Processing of Facial Expression. *Neuron*, 17(5), 875–887.
- Brugha, T. S., McManus, S., Bankart, J., Scott, F., Purdon, S., Smith, J., ... Meltzer, H. (2011). Epidemiology of Autism Spectrum Disorders in Adults in the Community in England. *Archives of General Psychiatry*, 68(5), 459.
- Büchel, C., Holmes, A., Rees, G., & Friston, K. (1998). Characterizing StimulusResponse Functions Using Nonlinear Regressors in Parametric fMRI Experiments. *NeuroImage*, 8(2), 140–148.
- Buckner, R. L. (1998). Event-related fMRI and the hemodynamic response. *Human brain mapping*, 6(5-6), 373–7.
- Button, K. S., Ioannidis, J. P. A., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., & Munafò, M. R. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience*, 14(5), 365–376.
- Bzdok, D., Laird, A. R., Zilles, K., Fox, P. T., & Eickhoff, S. B. (2013). An investigation of the structural, connectional, and functional subspecialization in the human amygdala. *Human Brain Mapping*, 34(12), 3247–3266.
- Bzdok, D., Langner, R., Schilbach, L., Jakobs, O., Roski, C., Caspers, S., ... Eickhoff, S. B. (2013). Characterization of the temporo-parietal junction by combining data-driven parcellation, complementary connectivity analyses, and functional decoding. *NeuroImage*, 81, 381–392.
- Caramazza, A., Anzellotti, S., Strnad, L., & Lingnau, A. (2014). Embodied Cognition and Mirror Neurons: A Critical Assessment. *Annual Review of Neuroscience*, 37(1), 1–15.
- Cardinal, R. N., Parkinson, J. A., Hall, J., & Everitt, B. J. (2002). Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. *Neuroscience and biobehavioral reviews*, 26(3), 321–52.
- Carelli, L., Solca, F., Faini, A., Meriggi, P., Sangalli, D., Cipresso, P., ... Poletti, B. (2017). Brain-Computer Interface for Clinical Purposes: Cognitive Assessment and Rehabilitation. *BioMed Research International*, 2017, 1–11.
- Carpenter, M., Nagell, K., & Tomasello, M. (1998). Social cognition, joint attention, and communicative competence from 9 to 15 months of age. *Monographs of the Society for Research in Child Development*, 63(4), i–vi, 1–143.
- Casile, A., & Giese, M. A. (2006). Nonvisual Motor Training Influences Biological Motion Perception. *Current Biology*, 16(1), 69–74.
- Caspers, S., Zilles, K., Laird, A. R., & Eickhoff, S. B. (2010). ALE meta-analysis of action observation and imitation in the human brain. *NeuroImage*, 50(3), 1148–1167.
- Castelli, F., Frith, C., Happé, F., & Frith, U. (2002). Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. *Brain*, 125(8), 1839–1849.
- Castelli, F., Happé, F., Frith, U., & Frith, C. (2000). Movement and Mind: A Functional Imaging Study of Perception and Interpretation of Complex Intentional Movement Patterns. *NeuroImage*, 12(3), 314–325.
- Castiello, U. (2003). Understanding other people's actions: intention and attention. *Journal of experimental psychology. Human perception and performance*, 29(2), 416–30.
- Cavallo, A., Catmur, C., Sowden, S., Iani, F., & Becchio, C. (2014). Stopping movements: when others slow us down. *European Journal of Neuroscience*, 40(5), 2842–2849.
- Chartrand, T. L., & Bargh, J. A. (1999). The chameleon effect: the perception-behavior link and social interaction. *Journal of personality and social psychology*, 76(6), 893–910.

BIBLIOGRAPHY

- Chartrand, T. L., & Lakin, J. L. (2013). The Antecedents and Consequences of Human Behavioral Mimicry. *Annual Review of Psychology*, 64(1), 285–308.
- Chauvigné, L. A. S., & Brown, S. (2018). Role-Specific Brain Activations in Leaders and Followers During Joint Action. *Frontiers in human neuroscience*, 12, 401.
- Chee, M. W., Venkatraman, V., Westphal, C., & Siong, S. C. (2003). Comparison of block and event-related fMRI designs in evaluating the word-frequency effect. *Human Brain Mapping*, 18(3), 186–193.
- Chen, T., Becker, B., Camilleri, J., Wang, L., Yu, S., Eickhoff, S. B., & Feng, C. (2018). A domain-general brain network underlying emotional and cognitive interference processing: evidence from coordinate-based and functional connectivity meta-analyses. *Brain Structure and Function*, 223(8), 3813–3840.
- Ciaramidaro, A., Becchio, C., Colle, L., Bara, B. G., & Walter, H. (2014). Do you mean me? Communicative intentions recruit the mirror and the mentalizing system. *Social cognitive and affective neuroscience*, 9(7), 909–16.
- Cisler, J. M., Bush, K., & Steele, J. S. (2014). A comparison of statistical methods for detecting context-modulated functional connectivity in fMRI. *NeuroImage*, 84, 1042–1052.
- Cohen, S., Masyn, K., Mastergeorge, A., & Hessl, D. (2015). Psychophysiological responses to emotional stimuli in children and adolescents with autism and fragile X syndrome. *Journal of clinical child and adolescent psychology: the official journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53*, 44(2), 250–63.
- Coleman-Fountain, E. (2017). Uneasy encounters: Youth, social (dis)comfort and the autistic self. *Social Science & Medicine*, 185, 9–16.
- Cook, J. (2016). From movement kinematics to social cognition: the case of autism. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 371(1693).
- Coqueugniot, H., Hublin, J.-J., Veillon, F., Houët, F., & Jacob, T. (2004). Early brain growth in Homo erectus and implications for cognitive ability. *Nature*, 431(7006), 299–302.
- Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, 3(3), 215–229.
- Datko, M., Pineda, J. A., & Müller, R.-A. (2018). Positive effects of neurofeedback on autism symptoms correlate with brain activation during imitation and observation. *European Journal of Neuroscience*, 47(6), 579–591.
- De Jaegher, H., Di Paolo, E., & Gallagher, S. (2010). Can social interaction constitute social cognition? *Trends in Cognitive Sciences*, 14(10), 441–447.
- Dehaene, S., Posner, M. I., & Tucker, D. M. (1994). Localization of a Neural System for Error Detection and Compensation. *Psychological Science*, 5(5), 303–305.
- DeMyer, M. K., Hingtgen, J. N., & Jackson, R. K. (1981). Infantile Autism Reviewed: A Decade of Research. *Schizophrenia Bulletin*, 7(3), 388–451.
- Di Russo, F., Lucci, G., Sulpizio, V., Berchicci, M., Spinelli, D., Pitzalis, S., & Galati, G. (2016). Spatiotemporal brain mapping during preparation, perception, and action. *NeuroImage*, 126, 1–14.
- Dichter, G. S. (2012). Functional magnetic resonance imaging of autism spectrum disorders. *Dialogues in Clinical Neuroscience*, 14(3), 319.
- Driver, J., Davis, G., Ricciardelli, P., Kidd, P., Maxwell, E., & Baron-Cohen, S. (1999). Gaze Perception Triggers Reflexive Visuospatial Orienting. *Visual Cognition*, 6(5), 509–540.
- Dufour, N., Redcay, E., Young, L., Mavros, P. L., Moran, J. M., Triantafyllou, C., ... Saxe, R. (2013). Similar Brain Activation during False Belief Tasks in a Large Sample of Adults with and without Autism. *PLoS ONE*, 8(9), e75468.
- Dumas, G., Chavez, M., Nadel, J., & Martinerie, J. (2012). Anatomical Connectivity Influences both Intra- and Inter-Brain Synchronizations. *PLoS ONE*, 7(5), e36414.

- Dumas, G., Nadel, J., Soussignan, R., Martinerie, J., & Garnero, L. (2010). Inter-Brain Synchronization during Social Interaction. *PLoS ONE*, *5*(8), e12166.
- Dumas, G., Zillekens, I. C., Lahnakoski, J. M., Vogeley, K., Tittgemeyer, M., & Schilbach, L. (2019). A social neuro-computational approach from intra- to inter-brain connectivity in autism. (Manuscript in preparation)
- Dwyer, D. B., Falkai, P., & Koutsouleris, N. (2018). Machine Learning Approaches for Clinical Psychology and Psychiatry. *Annual Review of Clinical Psychology*, *14*(1), 91–118.
- Engell, A. D., Nummenmaa, L., Oosterhof, N. N., Henson, R. N., Haxby, J. V., & Calder, A. J. (2010). Differential activation of frontoparietal attention networks by social and symbolic spatial cues. *Social cognitive and affective neuroscience*, *5*(4), 432–40.
- Fairhurst, M. T., Janata, P., & Keller, P. E. (2014). Leading the follower: An fMRI investigation of dynamic cooperativity and leader-follower strategies in synchronization with an adaptive virtual partner. *NeuroImage*, *84*, 688–697.
- Fehr, E., & Fischbacher, U. (2004). Third-party punishment and social norms. *Evolution and Human Behavior*, *25*(2), 63–87.
- Fischer, H., Furmark, T., Wik, G., & Fredrikson, M. (2000). Brain representation of habituation to repeated complex visual stimulation studied with PET. *NeuroReport*, *11*(1), 123–126.
- Fletcher-Watson, S., Leekam, S. R., Findlay, J. M., & Stanton, E. C. (2008). Brief Report: Young Adults with Autism Spectrum Disorder Show Normal Attention to Eye-Gaze Information Evidence from a New Change Blindness Paradigm. *Journal of Autism and Developmental Disorders*, *38*(9), 1785–1790.
- Frank, F., Jablotschkin, M., Arthen, T., Riedel, A., Fangmeier, T., Hölzel, L. P., & Tebartz van Elst, L. (2018). Education and employment status of adults with autism spectrum disorders in Germany a cross-sectional-survey. *BMC Psychiatry*, *18*(1), 75.
- Freitag, C. M. (2007). The genetics of autistic disorders and its clinical relevance: a review of the literature. *Molecular Psychiatry*, *12*(1), 2–22.
- Friedrich, E. V. C., Suttie, N., Sivanathan, A., Lim, T., Louchart, S., & Pineda, J. A. (2014). Brain-computer interface game applications for combined neurofeedback and biofeedback treatment for children on the autism spectrum. *Frontiers in Neuroengineering*, *7*, 21.
- Friedrich, E. V. C., Zillekens, I. C., Biel, A. L., Sauseng, P., & Schilbach, L. (2019). EEG correlates of the perception of communicative point-light stimuli. (Manuscript in preparation)
- Friesen, C. K., & Kingstone, A. (1998). The eyes have it! Reflexive orienting is triggered by nonpredictive gaze. *Psychonomic Bulletin & Review*, *5*(3), 490–495.
- Friston, K. (2002). Functional integration and inference in the brain. *Progress in neurobiology*, *68*(2), 113–43.
- Friston, K. (2003). Learning and inference in the brain. *Neural Networks*, *16*(9), 1325–1352.
- Friston, K. (2005). A theory of cortical responses. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *360*(1456), 815–836.
- Friston, K. (2009). Modalities, Modes, and Models in Functional Neuroimaging. *Science*, *326*(5951), 399–403.
- Friston, K., Fletcher, P., Josephs, O., Holmes, A., Rugg, M., & Turner, R. (1998). Event-Related fMRI: Characterizing Differential Responses. *NeuroImage*, *7*(1), 30–40.
- Frith, C. D., & Frith, U. (2008). Implicit and Explicit Processes in Social Cognition. *Neuron*, *60*(3), 503–510.
- Frith, C. D., & Frith, U. (2012). Mechanisms of Social Cognition. *Annual Review of Psychology*, *63*(1), 287–313.
- Frith, U. (2001). Mind Blindness and the Brain in Autism. *Neuron*, *32*(6), 969–979.

BIBLIOGRAPHY

- Geurts, H. M., van den Bergh, S. F. W. M., & Ruzzano, L. (2014). Prepotent Response Inhibition and Interference Control in Autism Spectrum Disorders: Two Meta-Analyses. *Autism Research*, 7(4), 407–420.
- Gibbard, C. R., Ren, J., Skuse, D. H., Clayden, J. D., & Clark, C. A. (2018). Structural connectivity of the amygdala in young adults with autism spectrum disorder. *Human Brain Mapping*, 39(3), 1270–1282.
- Giese, M. A., & Poggio, T. (2003). Neural mechanisms for the recognition of biological movements. *Nature Reviews Neuroscience*, 4(3), 179–192.
- Glerean, E., Pan, R. K., Salmi, J., Kujala, R., Lahnakoski, J. M., Roine, U., ... Jääskeläinen, I. P. (2016). Reorganization of functionally connected brain subnetworks in high-functioning autism. *Human Brain Mapping*, 37(3), 1066–1079.
- Gómez, C., Lizier, J. T., Schaum, M., Wollstadt, P., Grützner, C., Uhlhaas, P., ... Wibral, M. (2014). Reduced predictable information in brain signals in autism spectrum disorder. *Frontiers in Neuroinformatics*, 8, 9.
- Greenough, W. T., Black, J. E., & Wallace, C. S. (1987). Experience and brain development. *Child development*, 58(3), 539–59.
- Haker, H., Schneebeli, M., & Stephan, K. E. (2016). Can Bayesian Theories of Autism Spectrum Disorder Help Improve Clinical Practice? *Frontiers in Psychiatry*, 7, 107.
- Hämäläinen, M., Hari, R., Ilmoniemi, R. J., Knuutila, J., & Lounasmaa, O. V. (1993). Magnetoencephalography theory, instrumentation, and applications to noninvasive studies of the working human brain. *Reviews of Modern Physics*, 65(2), 413–497.
- Hari, R., & Kujala, M. V. (2009). Brain Basis of Human Social Interaction: From Concepts to Brain Imaging. *Physiological Reviews*, 89(2), 453–479.
- Hashimoto, Y., & Sakai, K. L. (2003). Brain activations during conscious self-monitoring of speech production with delayed auditory feedback: An fMRI study. *Human Brain Mapping*, 20(1), 22–28.
- Hasson, U., Avidan, G., Gelbard, H., Vallines, I., Harel, M., Minshew, N., & Behrmann, M. (2009). Shared and idiosyncratic cortical activation patterns in autism revealed under continuous real-life viewing conditions. *Autism Research*, 2(4), 220–231.
- Haxby, J. V., Hoffman, E. A., & Gobbini, M. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences*, 4(6), 223–233.
- Heider, F., & Simmel, M. (1944). An Experimental Study of Apparent Behavior. *The American Journal of Psychology*, 57(2), 243.
- Hietanen, J. K., Nummenmaa, L., Nyman, M. J., Parkkola, R., & Hämäläinen, H. (2006). Automatic attention orienting by social and symbolic cues activates different neural networks: An fMRI study. *NeuroImage*, 33(1), 406–413.
- Hofvander, B., Delorme, R., Chaste, P., Nydén, A., Wentz, E., Ståhlberg, O., ... Leboyer, M. (2009). Psychiatric and psychosocial problems in adults with normal-intelligence autism spectrum disorders. *BMC Psychiatry*, 9(1), 35.
- Holland, D., Chang, L., Ernst, T. M., Curran, M., Buchthal, S. D., Alicata, D., ... Dale, A. M. (2014). Structural Growth Trajectories and Rates of Change in the First 3 Months of Infant Brain Development. *JAMA Neurology*, 71(10), 1266.
- Holler, J., Kokal, I., Toni, I., Hagoort, P., Kelly, S. D., & Özyürek, A. (2015). Eye'm talking to you: speakers' gaze direction modulates co-speech gesture processing in the right MTG. *Social Cognitive and Affective Neuroscience*, 10(2), 255–261.
- Hommel, B., Fischer, R., Colzato, L. S., van den Wildenberg, W. P. M., & Cellini, C. (2012). The effect of fMRI (noise) on cognitive control. *Journal of Experimental Psychology: Human Perception and Performance*, 38(2), 290–301.

- Hove, M. J., & Risen, J. L. (2009). It's All in the Timing: Interpersonal Synchrony Increases Affiliation. *Social Cognition*, 27(6), 949–960.
- Howlin, P., & Magiati, I. (2017). Autism spectrum disorder. *Current Opinion in Psychiatry*, 30(2), 69–76.
- Huttenlocher, P. R. (1990). Morphometric study of human cerebral cortex development. *Neuropsychologia*, 28(6), 517–27.
- Iidaka, T., Kogata, T., Mano, Y., & Komeda, H. (2019). Thalamocortical Hyperconnectivity and Amygdala–Cortical Hypoconnectivity in Male Patients With Autism Spectrum Disorder. *Frontiers in Psychiatry*, 10, 252.
- James, I. A., Mukaetova-Ladinska, E., Reichelt, F. K., Briel, R., & Scully, A. (2006). Diagnosing Aspergers syndrome in the elderly: a series of case presentations. *International Journal of Geriatric Psychiatry*, 21(10), 951–960.
- Johansson, G. (1973). Visual perception of biological motion and a model for its analysis. *Perception & Psychophysics*, 14(2), 201–211.
- Johnson, M. H. (2005). Subcortical face processing. *Nature Reviews Neuroscience*, 6(10), 766–774.
- Joseph, R. M., Fricker, Z., & Keehn, B. (2015). Activation of frontoparietal attention networks by non-predictive gaze and arrow cues. *Social Cognitive and Affective Neuroscience*, 10(2), 294–301.
- Kana, R. K., Keller, T. A., Cherkassky, V. L., Minshew, N. J., & Just, M. A. (2009). Atypical frontal-posterior synchronization of Theory of Mind regions in autism during mental state attribution. *Social Neuroscience*, 4(2), 135–152.
- Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child*, 2, 217–250.
- Kapur, S., Phillips, A. G., & Insel, T. R. (2012). Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Molecular Psychiatry*, 17(12), 1174–1179.
- Kastner, P. (2017). *ElegantThesisLaTeX*. (Retrieved on August 2, 2019 from <https://github.com/kastnerp/ElegantThesisLaTeX>)
- Kendon, A. (1970). Movement coordination in social interaction: some examples described. *Acta psychologica*, 32(2), 100–25.
- Kilner, J., Hamilton, A. F., & Blakemore, S.-J. (2007). Interference effect of observed human movement on action is due to velocity profile of biological motion. *Social Neuroscience*, 2(3-4), 158–166.
- Kirchner, J. C., & Dziobek, I. (2014). Toward the Successful Employment of Adults with Autism: A First Analysis of Special Interests and Factors Deemed Important for Vocational Performance. *Scandinavian Journal of Child and Adolescent Psychiatry and Psychology*, 2(2), 77–85.
- Kirsch, L. P., Drommelschmidt, K. A., & Cross, E. S. (2013). The impact of sensorimotor experience on affective evaluation of dance. *Frontiers in human neuroscience*, 7, 521.
- Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Archives of general psychiatry*, 59(9), 809–16.
- Klucharev, V., Hytönen, K., Rijpkema, M., Smidts, A., & Fernández, G. (2009). Reinforcement Learning Signal Predicts Social Conformity. *Neuron*, 61(1), 140–151.
- Klusek, J., Martin, G. E., & Losh, M. (2013). Physiological Arousal in Autism and Fragile X Syndrome: Group Comparisons and Links With Pragmatic Language. *American Journal on Intellectual and Developmental Disabilities*, 118(6), 475–495.
- Knoblich, G., & Sebanz, N. (2006). The Social Nature of Perception and Action. *Current Directions in Psychological Science*, 15(3), 99–104.
- Koechlin, E., Corrado, G., Pietrini, P., & Grafman, J. (2000). Dissociating the role of the medial and lateral anterior prefrontal cortex in human planning. *Proceedings of the National Academy*

BIBLIOGRAPHY

- of *Sciences*, 97(13), 7651–7656.
- Körding, K. P., & Wolpert, D. M. (2004). Bayesian integration in sensorimotor learning. *Nature*, 427(6971), 244–247.
- Kuramoto, Y. (1975). Self-entrainment of a population of coupled non-linear oscillators. In *International symposium on mathematical problems in theoretical physics* (pp. 420–422). Berlin/Heidelberg: Springer-Verlag.
- Lai, M.-C., Lombardo, M. V., & Baron-Cohen, S. (2014). Autism. *The Lancet*, 383(9920), 896–910.
- Lee, W. H., & Frangou, S. (2017). Linking functional connectivity and dynamic properties of resting-state networks. *Scientific reports*, 7(1), 16610.
- Levy, J., Goldstein, A., & Feldman, R. (2019). The neural development of empathy is sensitive to caregiving and early trauma. *Nature Communications*, 10(1), 1905.
- Logothetis, N. K. (2002). The neural basis of the bloodoxygenleveldependent functional magnetic resonance imaging signal. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, 357(1424), 1003–1037.
- Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. *Nature*, 453(7197), 869–878.
- Loth, E., Gómez, J. C., & Happé, F. (2011). Do High-Functioning People with Autism Spectrum Disorder Spontaneously Use Event Knowledge to Selectively Attend to and Remember Context-Relevant Aspects in Scenes? *Journal of Autism and Developmental Disorders*, 41(7), 945–961.
- Macrae, C. N., Duffy, O. K., Miles, L. K., & Lawrence, J. (2008). A case of hand waving: Action synchrony and person perception. *Cognition*, 109(1), 152–156.
- Majerus, S., Péters, F., Bouffier, M., Cowan, N., & Phillips, C. (2018). The Dorsal Attention Network Reflects Both Encoding Load and Topdown Control during Working Memory. *Journal of Cognitive Neuroscience*, 30(2), 144–159.
- Manera, V., Becchio, C., Cavallo, A., Sartori, L., & Castiello, U. (2011). Cooperation or competition? Discriminating between social intentions by observing prehensile movements. *Experimental brain research*, 211(3-4), 547–56.
- Manera, V., Becchio, C., Schouten, B., Bara, B. G., & Verfaillie, K. (2011). Communicative Interactions Improve Visual Detection of Biological Motion. *PLoS ONE*, 6(1), e14594.
- Manera, V., Del Giudice, M., Bara, B. G., Verfaillie, K., & Becchio, C. (2011). The Second-Agent Effect: Communicative Gestures Increase the Likelihood of Perceiving a Second Agent. *PLoS ONE*, 6(7), e22650.
- Manera, V., Schouten, B., Becchio, C., Bara, B. G., & Verfaillie, K. (2010). Inferring intentions from biological motion: A stimulus set of point-light communicative interactions. *Behavior Research Methods*, 42(1), 168–178.
- Manera, V., Schouten, B., Verfaillie, K., & Becchio, C. (2013). Time will show: real time predictions during interpersonal action perception. *PloS one*, 8(1), e54949.
- Marco, E. J., Hinkley, L. B. N., Hill, S. S., & Nagarajan, S. S. (2011). Sensory processing in autism: a review of neurophysiologic findings. *Pediatric research*, 69(5 Pt 2), 48R–54R.
- Marsh, K. L., Isenhower, R. W., Richardson, M. J., Helt, M., Verbalis, A. D., Schmidt, R. C., & Fein, D. (2013). Autism and social disconnection in interpersonal rocking. *Frontiers in Integrative Neuroscience*, 7, 4.
- Marsh, K. L., Richardson, M. J., & Schmidt, R. C. (2009). Social connection through joint action and interpersonal coordination. *Topics in cognitive science*, 1(2), 320–39.
- Marsh, L. E., & Hamilton, A. F. (2011). Dissociation of mirroring and mentalising systems in autism. *NeuroImage*, 56(3), 1511–1519.
- Maximo, J. O., Cadena, E. J., & Kana, R. K. (2014). The Implications of Brain Connectivity in the Neuropsychology of Autism. *Neuropsychology Review*, 24(1), 16–31.

- Mechelli, A., Henson, R. N. A., Price, C. J., & Friston, K. J. (2003). Comparing event-related and epoch analysis in blocked design fMRI. *NeuroImage*, *18*(3), 806–10.
- Minschew, N. J., & Keller, T. A. (2010). The nature of brain dysfunction in autism: functional brain imaging studies. *Current opinion in neurology*, *23*(2), 124–30.
- Moriuchi, J. M., Klin, A., & Jones, W. (2017). Mechanisms of Diminished Attention to Eyes in Autism. *American Journal of Psychiatry*, *174*(1), 26–35.
- Muhle, R., Trentacoste, S. V., & Rapin, I. (2004). The Genetics of Autism. *Pediatrics*, *113*(5), e472–e486.
- Müller, E., Schuler, A., & Yates, G. B. (2008). Social challenges and supports from the perspective of individuals with Asperger syndrome and other autism spectrum disabilities. *Autism*, *12*(2), 173–190.
- Mundy, P., Sigman, M., Ungerer, J., & Sherman, T. (1986). Defining the social deficits of autism: the contribution of non-verbal communication measures. *Journal of Child Psychology and Psychiatry*, *27*(5), 657–669.
- Neri, P., Luu, J. Y., & Levi, D. M. (2006). Meaningful interactions can enhance visual discrimination of human agents. *Nature Neuroscience*, *9*(9), 1186–1192.
- Newman-Norlund, R. D., van Schie, H. T., van Zuijlen, A. M. J., & Bekkering, H. (2007). The mirror neuron system is more active during complementary compared with imitative action. *Nature Neuroscience* 2007 10:7, *10*(7), 817.
- Nigg, J. T. (2000). On inhibition/disinhibition in developmental psychopathology: views from cognitive and personality psychology and a working inhibition taxonomy. *Psychological bulletin*, *126*(2), 220–46.
- Nummenmaa, L., & Calder, A. J. (2009). Neural mechanisms of social attention. *Trends in Cognitive Sciences*, *13*(3), 135–143.
- Nummenmaa, L., Passamonti, L., Rowe, J., Engell, A. D., & Calder, A. J. (2010). Connectivity analysis reveals a cortical network for eye gaze perception. *Cerebral cortex (New York, N.Y. : 1991)*, *20*(8), 1780–7.
- Okruszek, Ł., Piejka, A., Wysokiński, A., Szczepocka, E., & Manera, V. (2017). The second agent effect: Interpersonal predictive coding in people with schizophrenia. *Social Neuroscience*, 1–6.
- Orsmond, G. I., Shattuck, P. T., Cooper, B. P., Sterzing, P. R., & Anderson, K. A. (2013). Social Participation Among Young Adults with an Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *43*(11), 2710–2719.
- Padmanabhan, A., Lynch, C. J., Schaer, M., & Menon, V. (2017). The Default Mode Network in Autism. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *2*(6), 476–486.
- Pavlova, M. A. (2012). Biological motion processing as a hallmark of social cognition. *Cerebral cortex (New York, N.Y. : 1991)*, *22*(5), 981–95.
- Pavlova, M. A., Erb, M., Hagberg, G. E., Loureiro, J., Sokolov, A. N., & Scheffler, K. (2017). Wrong Way Up: Temporal and Spatial Dynamics of the Networks for Body Motion Processing at 9.4 T. *Cerebral Cortex*, *27*(11), 5318–5330.
- Pellicano, E., & Burr, D. (2012). When the world becomes too real: a Bayesian explanation of autistic perception. *Trends in Cognitive Sciences*, *16*(10), 504–510.
- Pelphrey, K. A., Morris, J. P., & McCarthy, G. (2005). Neural basis of eye gaze processing deficits in autism. *Brain*, *128*(5), 1038–1048.
- Pelphrey, K. A., Singerman, J. D., Allison, T., & McCarthy, G. (2003). Brain activation evoked by perception of gaze shifts: the influence of context. *Neuropsychologia*, *41*(2), 156–70.
- Peterson, C. C., Slaughter, V. P., & Paynter, J. (2007). Social maturity and theory of mind in typically developing children and those on the autism spectrum. *Journal of Child Psychology and Psychiatry*, *48*(12), 1243–1250.

BIBLIOGRAPHY

- Pfeiffer, U. J., Schilbach, L., Timmermans, B., Kuzmanovic, B., Georgescu, A. L., Bente, G., & Vogeley, K. (2014). Why we interact: On the functional role of the striatum in the subjective experience of social interaction. *NeuroImage*, *101*, 124–137.
- Pickering, M. J., & Garrod, S. (2013). An integrated theory of language production and comprehension. *Behavioral and Brain Sciences*, *36*(4), 329–347.
- Pierno, A. C., Becchio, C., Tubaldi, F., Turella, L., & Castiello, U. (2008). Motor ontology in representing gazeobject relations. *Neuroscience Letters*, *430*(3), 246–251.
- Pierno, A. C., Becchio, C., Wall, M. B., Smith, A. T., Turella, L., & Castiello, U. (2006). When Gaze Turns into Grasp. *Journal of Cognitive Neuroscience*, *18*(12), 2130–2137.
- Pitskel, N. B., Bolling, D. Z., Hudac, C. M., Lantz, S. D., Minshew, N. J., Vander Wyk, B. C., & Pelphrey, K. A. (2011). Brain mechanisms for processing direct and averted gaze in individuals with autism. *Journal of autism and developmental disorders*, *41*(12), 1686–93.
- Poldrack, R. A. (2011). Inferring mental states from neuroimaging data: from reverse inference to large-scale decoding. *Neuron*, *72*(5), 692–7.
- Pönkänen, L. M., Alhoniemi, A., Leppänen, J. M., & Hietanen, J. K. (2011). Does it make a difference if I have an eye contact with you or with your picture? An ERP study. *Social Cognitive and Affective Neuroscience*, *6*(4), 486–494.
- Prinsen, J., Bernaerts, S., Wang, Y., de Beukelaar, T. T., Cuypers, K., Swinnen, S. P., & Alaerts, K. (2017). Direct eye contact enhances mirroring of others' movements: A transcranial magnetic stimulation study. *Neuropsychologia*, *95*, 111–118.
- Raichle, M. E. (2009). A brief history of human brain mapping. *Trends in Neurosciences*, *32*(2), 118–126.
- Ramot, M., Kimmich, S., Gonzalez-Castillo, J., Roopchansingh, V., Popal, H., White, E., ... Martin, A. (2017). Direct modulation of aberrant brain network connectivity through real-time NeuroFeedback. *eLife*, *6*.
- Redcay, E., & Schilbach, L. (2019). Using second-person neuroscience to elucidate the mechanisms of social interaction. *Nature Reviews Neuroscience*, *1*.
- Rendell, L., Boyd, R., Cownden, D., Enquist, M., Eriksson, K., Feldman, M. W., ... Laland, K. N. (2010). Why copy others? Insights from the social learning strategies tournament. *Science (New York, N.Y.)*, *328*(5975), 208–13.
- Richardson, M. J., Marsh, K. L., & Schmidt, R. C. (2005). Effects of Visual and Verbal Interaction on Unintentional Interpersonal Coordination. *Journal of Experimental Psychology: Human Perception and Performance*, *31*(1), 62–79.
- Rizzolatti, G., & Craighero, L. (2004). The mirror-neuron system. *Annual Review of Neuroscience*, *27*(1), 169–192.
- Rizzolatti, G., Fadiga, L., Fogassi, L., & Gallese, V. (1999). Resonance behaviors and mirror neurons. *Archives italiennes de biologie*, *137*(2-3), 85–100.
- Ronald, A., & Hoekstra, R. A. (2011). Autism spectrum disorders and autistic traits: A decade of new twin studies. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *156*(3), 255–274.
- Salmi, J., Roine, U., Glerean, E., Lahnakoski, J., Nieminen-von Wendt, T., Tani, P., ... Sams, M. (2013). The brains of high functioning autistic individuals do not synchronize with those of others. *NeuroImage: Clinical*, *3*, 489–497.
- Santangelo, S. L., & Tsatsanis, K. (2005). What is known about autism: genes, brain, and behavior. *American journal of pharmacogenomics : genomics-related research in drug development and clinical practice*, *5*(2), 71–92.
- Santiesteban, I., Banissy, M., Catmur, C., & Bird, G. (2012). Enhancing Social Ability by Stimulating Right Temporoparietal Junction. *Current Biology*, *22*(23), 2274–2277.

- Santiesteban, I., Banissy, M. J., Catmur, C., & Bird, G. (2015). Functional lateralization of temporoparietal junction - imitation inhibition, visual perspective-taking and theory of mind. *European Journal of Neuroscience*, *42*(8), 2527–2533.
- Sapey-Triomphe, L.-A., Centelles, L., Roth, M., Fonlupt, P., Hénaff, M.-A., Schmitz, C., & Assaiante, C. (2016). Deciphering human motion to discriminate social interactions: a developmental neuroimaging study. *Social Cognitive and Affective Neuroscience*, *12*(2), nsw117.
- Sartori, L., & Betti, S. (2015). Complementary actions. *Frontiers in psychology*, *6*, 557.
- Sato, W., & Uono, S. (2019). The atypical social brain network in autism. *Current Opinion in Neurology*, *32*(4), 617–621.
- Satpute, A. B., & Lieberman, M. D. (2006). Integrating automatic and controlled processes into neurocognitive models of social cognition. *Brain Research*, *1079*(1), 86–97.
- Saygin, A. P., Wilson, S. M., Hagler, D. J., Bates, E., & Sereno, M. I. (2004). Point-Light Biological Motion Perception Activates Human Premotor Cortex. *Journal of Neuroscience*, *24*(27), 6181–6188.
- Schilbach, L. (2016). Towards a second-person neuropsychiatry. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, *371*(1686), 20150081.
- Schilbach, L., Eickhoff, S. B., Cieslik, E., Shah, N. J., Fink, G. R., & Vogeley, K. (2011). Eyes on me: an fMRI study of the effects of social gaze on action control. *Social Cognitive and Affective Neuroscience*, *6*(4), 393–403.
- Schilbach, L., Eickhoff, S. B., Cieslik, E. C., Kuzmanovic, B., & Vogeley, K. (2012). Shall we do this together? Social gaze influences action control in a comparison group, but not in individuals with high-functioning autism. *Autism*, *16*(2), 151–162.
- Schilbach, L., Timmermans, B., Reddy, V., Costall, A., Bente, G., Schlicht, T., & Vogeley, K. (2013). Toward a second-person neuroscience. *Behavioral and Brain Sciences*, *36*(4), 393–414.
- Schilbach, L., Wohlschlaeger, A. M., Kraemer, N. C., Newen, A., Shah, N. J., Fink, G. R., & Vogeley, K. (2006). Being with virtual others: Neural correlates of social interaction. *Neuropsychologia*, *44*(5), 718–730.
- Schmidt, L., Kirchner, J., Strunz, S., Brożus, J., Ritter, K., Roepke, S., & Dziobek, I. (2015). Psychosocial Functioning and Life Satisfaction in Adults With Autism Spectrum Disorder Without Intellectual Impairment. *Journal of Clinical Psychology*, *71*(12), 1259–1268.
- Schmitz, N., Rubia, K., Daly, E., Smith, A., Williams, S., & Murphy, D. G. (2006). Neural Correlates of Executive Function in Autistic Spectrum Disorders. *Biological Psychiatry*, *59*(1), 7–16.
- Schneider, D., Slaughter, V. P., Bayliss, A. P., & Dux, P. E. (2013). A temporally sustained implicit theory of mind deficit in autism spectrum disorders. *Cognition*, *129*(2), 410–417.
- Schobert, A.-K., Corradi-Dell'Acqua, C., Frühholz, S., van der Zwaag, W., & Vuilleumier, P. (2018). Functional organization of face processing in the human superior temporal sulcus: a 7T high-resolution fMRI study. *Social cognitive and affective neuroscience*, *13*(1), 102–113.
- Schulz, K. P., Clerkin, S. M., Halperin, J. M., Newcorn, J. H., Tang, C. Y., & Fan, J. (2009). Dissociable neural effects of stimulus valence and preceding context during the inhibition of responses to emotional faces. *Human Brain Mapping*, *30*(9), 2821–2833.
- Senju, A. (2012). Spontaneous Theory of Mind and Its Absence in Autism Spectrum Disorders. *The Neuroscientist*, *18*(2), 108–113.
- Senju, A., & Johnson, M. H. (2009a). The eye contact effect: mechanisms and development. *Trends in Cognitive Sciences*, *13*(3), 127–134.
- Senju, A., & Johnson, M. H. (2009b). The eye contact effect: mechanisms and development. *Trends in Cognitive Sciences*, *13*(3), 127–134.
- Senju, A., Southgate, V., White, S., & Frith, U. (2009). Mindblind Eyes: An Absence of Spontaneous Theory of Mind in Asperger Syndrome. *Science*, *325*(5942), 883–885.

BIBLIOGRAPHY

- Senju, A., Tojo, Y., Dairoku, H., & Hasegawa, T. (2004). Reflexive orienting in response to eye gaze and an arrow in children with and without autism. *Journal of Child Psychology and Psychiatry*, *45*(3), 445–458.
- Shultz, S., Klin, A., & Jones, W. (2018). Neonatal Transitions in Social Behavior and Their Implications for Autism. *Trends in Cognitive Sciences*, *22*(5), 452–469.
- Simon, J. R. (1969). Reactions toward the source of stimulation. *Journal of experimental psychology*, *81*(1), 174–6.
- Sowden, S., Wright, G., Banissy, M., Catmur, C., & Bird, G. (2015). Transcranial Current Stimulation of the Temporoparietal Junction Improves Lie Detection. *Current Biology*, *25*(18), 2447–2451.
- Stanislaw, H., & Todorov, N. (1999). Calculation of signal detection theory measures. *Behavior Research Methods, Instruments, & Computers*, *31*(1), 137–149.
- Sun, X., Allison, C., Wei, L., Matthews, F. E., Auyeung, B., Wu, Y., ... Brayne, C. (2019). Autism prevalence in China is comparable to Western prevalence. *Molecular Autism*, *10*(1), 7.
- Swettenham, J., Condie, S., Campbell, R., Milne, E., & Coleman, M. (2003). Does the perception of moving eyes trigger reflexive visual orienting in autism? *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *358*(1430), 325–334.
- Tanaka, J. W., & Sung, A. (2016). The Eye Avoidance Hypothesis of Autism Face Processing. *Journal of Autism and Developmental Disorders*, *46*(5), 1538–1552.
- Taylor, A. J., Kim, J. H., & Ress, D. (2018). Characterization of the hemodynamic response function across the majority of human cerebral cortex. *NeuroImage*, *173*, 322–331.
- Todorov, E., & Jordan, M. I. (2002). Optimal feedback control as a theory of motor coordination. *Nature Neuroscience*, *5*(11), 1226–1235.
- Top Jr., D. N., Luke, S. G., Stephenson, K. G., & South, M. (2019). Psychophysiological Arousal and Auditory Sensitivity in a Cross-Clinical Sample of Autistic and Non-autistic Anxious Adults. *Frontiers in Psychiatry*, *9*, 783.
- Topol, E. J. (2019). High-performance medicine: the convergence of human and artificial intelligence. *Nature Medicine*, *25*(1), 44–56.
- Trusheim, M. R., Berndt, E. R., & Douglas, F. L. (2007). Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. *Nature Reviews Drug Discovery*, *6*(4), 287–293.
- Underwood, A. G., Guynn, M. J., & Cohen, A.-L. (2015). The Future Orientation of Past Memory: The Role of BA 10 in Prospective and Retrospective Retrieval Modes. *Frontiers in Human Neuroscience*, *9*, 668.
- van Maanen, L., Forstmann, B. U., Keuken, M. C., Wagenmakers, E.-J., & Heathcote, A. (2016). The impact of MRI scanner environment on perceptual decision-making. *Behavior research methods*, *48*(1), 184–200.
- van Niekerk, M. E., Groen, W., Vissers, C. T., van Driel-de Jong, D., Kan, C. C., & Oude Voshaar, R. C. (2011). Diagnosing autism spectrum disorders in elderly people. *International Psychogeriatrics*, *23*(5), 700–710.
- Varlet, M., Marin, L., Lagarde, J., & Bardy, B. G. (2011). Social postural coordination. *Journal of Experimental Psychology: Human Perception and Performance*, *37*(2), 473–483.
- Vidal, F., Hasbroucq, T., Grapperon, J., & Bonnet, M. (2000). Is the 'error negativity' specific to errors? *Biological psychology*, *51*(2-3), 109–28.
- von dem Hagen, E. A. H., & Bright, N. (2017). High autistic trait individuals do not modulate gaze behaviour in response to social presence but look away more when actively engaged in an interaction. *Autism research : official journal of the International Society for Autism Research*, *10*(2), 359–368.

- von der Lühe, T., Manera, V., Barisic, I., Becchio, C., Vogeley, K., & Schilbach, L. (2016). Interpersonal predictive coding, not action perception, is impaired in autism. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 371(1693).
- Vossel, S., Weidner, R., Driver, J., Friston, K. J., & Fink, G. R. (2012). Deconstructing the architecture of dorsal and ventral attention systems with dynamic causal modeling. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 32(31), 10637–48.
- Wang, Y., & Hamilton, A. F. (2012). Social top-down response modulation (STORM): a model of the control of mimicry in social interaction. *Frontiers in Human Neuroscience*, 6, 153.
- Wang, Y., Ramsey, R., & Hamilton, A. F. (2011). The Control of Mimicry by Eye Contact Is Mediated by Medial Prefrontal Cortex. *Journal of Neuroscience*, 31(33), 12001–12010.
- Weilnhammer, V., Stuke, H., Hesselmann, G., Sterzer, P., & Schmack, K. (2017). A predictive coding account of bistable perception - a model-based fMRI study. *PLOS Computational Biology*, 13(5), e1005536.
- White, S. W., & Roberson-Nay, R. (2009). Anxiety, Social Deficits, and Loneliness in Youth with Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, 39(7), 1006–1013.
- Wood, J. N., Knutson, K. M., & Grafman, J. (2004). Psychological Structure and Neural Correlates of Event Knowledge. *Cerebral Cortex*, 15(8), 1155–1161.
- Woodman, A. C., Smith, L. E., Greenberg, J. S., & Mailick, M. R. (2016). Contextual Factors Predict Patterns of Change in Functioning over 10 Years Among Adolescents and Adults with Autism Spectrum Disorders. *Journal of autism and developmental disorders*, 46(1), 176–189.
- Yang, D. Y.-J., Rosenblau, G., Keifer, C., & Pelphrey, K. A. (2015). An integrative neural model of social perception, action observation, and theory of mind. *Neuroscience and biobehavioral reviews*, 51, 263–75.
- Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, D. C., & Wager, T. D. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nature methods*, 8(8), 665–70.
- Zalla, T., Labruyère, N., Clément, A., & Georgieff, N. (2010). Predicting ensuing actions in children and adolescents with autism spectrum disorders. *Experimental Brain Research*, 201(4), 809–819.
- Zalla, T., Labruyere, N., & Georgieff, N. (2006). Goal-Directed Action Representation in Autism. *Journal of Autism and Developmental Disorders*, 36(4), 527–540.
- Zhang, R., Geng, X., & Lee, T. M. C. (2017). Large-scale functional neural network correlates of response inhibition: an fMRI meta-analysis. *Brain Structure and Function*, 222(9), 3973–3990.
- Zillekens, I. C., Brandi, M.-L., Lahnakoski, J. M., Koul, A., Manera, V., Becchio, C., & Schilbach, L. (2019). Increased functional coupling of the left amygdala and medial prefrontal cortex during the perception of communicative point-light stimuli. *Social Cognitive and Affective Neuroscience*, 14(1), 97–107.
- Zillekens, I. C., Schliephake, L. M., Brandi, M.-L., & Schilbach, L. (2019). A look at actions: Direct gaze modulates functional connectivity of the right TPJ with an action control network. *Social Cognitive and Affective Neuroscience*. (Advance online publication. doi:10.1093/scan/nsz071)

Acknowledgments

The successful completion of this thesis would not have been possible without the support of many people. First, I would like to thank my first supervisor Leo Schilbach. I am very grateful for both his professional and personal support. From the first meeting onwards, his drive and creativity has been very inspiring and motivating. I am very thankful for the trust he has put into me, allowing me to work very independently and to grow as a researcher and as an individual. Furthermore, I would like to thank Nikos Koutsouleris for his contribution as member of my thesis advisory committee (TAC) and second expert of this thesis. In particular, I am very thankful for the invitation to take part in the 2017 PRONIA spring school, which triggered my interest in machine learning and, thus, has already had a considerable impact on my research. Next, I would like to thank Bettina Schönherr and Michael Mende for their support and advice. I highly appreciate the opportunities offered by the International Max Planck Research School for Translational Psychiatry and the funding as well as the infrastructure provided by the Max Planck Institute of Psychiatry. Moreover, I would like to thank PD. Dr. Andrea Jobst and Prof. Dr. Kathrin Koch for their immediate consent to review this thesis.

At this point, I would like to thank Marie-Luise Brandi. As a member of my TAC, co-author of both papers presented in this thesis and key figure for me in our research group, her impact on this thesis has been immense. I am deeply grateful for having given the chance to work with a colleague that warm-hearted and a researcher that competent. Further thanks go to my colleagues: Juha, thank you for your meticulous attention to detail as a co-author (in both the best and worst imaginable way). It's good to know that there are researchers in our field who stand up for their ideals and conduct science of highest quality. Lara and Luise, thank you for many hours at the MR scanner. Luise, Lara and Laura, thank you for the enriching exchanges and your mental support. Lena, thank you for making me feel welcomed in Munich from day one. Thanks all of you for your support and the fruitful collaborations.

Special thanks also go to Ines Eidner for her expertise and calmness at the MR scanner, as well as Anna Gallner. I would like to thank Heike Junkert and Nicole Grodzycki, who have always been knowledgeable and supportive. I am very thankful to Benno Pütz and Herbert Steininger being the last resort against MatLab or Linux crises. Eventually, I would like to take this opportunity to thank Shalaila Haas and Patrick Kastner. Their sophisticated \LaTeX template (Kastner, 2017) greatly helped me in formatting this thesis. Last but not least, I am very grateful to my partner and my family, in particular my mother and my sister, for their enduring support.

Publications

PUBLISHED

Zillekens, I. C., Brandi, M.-L., Lahnakoski, J. M., Koul, A., Manera, V., Becchio, C., & Schilbach, L. (2019). Increased functional coupling of the left amygdala and medial prefrontal cortex during the perception of communicative point-light stimuli. *Social cognitive and affective neuroscience*, 14(1): 97107.

Zillekens, I. C., Schliephake, L.M., Brandi, M.-L., & Schilbach, L. (2019). A look at actions: Direct gaze modulates functional connectivity of the right TPJ with an action control network. *Social cognitive and affective neuroscience*. (Advance online publication. doi:10.1093/scan/nsz071)

Albantakis, L., Parpart, H., Thaler, H., Krankenhagen, M., Böhm, J., **Zillekens, I. C.**, & Schilbach, L. (2018). Depression bei Erwachsenen mit Autismus-Spektrum-Störung. *Nervenheilkunde*, 37(09): 587-593.

Zillekens, I. C., & Schilbach, L. (2018). A measuring stick for other minds: : Comment on 'Seeing mental states: An experimental strategy for measuring the observability of other minds' by Cristina Becchio et al. *Phys Life Rev*, 24:101-103.

IN PREPARATION

Albantakis, L., Brandi, M.-L., **Zillekens, I. C.**, Henco, L., Weindl, L., Thaler, H., Schliephake, L. M., Timmermans, B. & Schilbach, L. (2019). Comorbidities in autism are associated with the co-occurrence of alexithymia. (Manuscript in preparation)

Dumas, G., **Zillekens, I. C.**, Lahnakoski, J. M., Vogeley, K., Tittgemeyer, M., & Schilbach, L. (2019). A social neuro-computational approach from intra- to inter-brain connectivity in autism. (Manuscript in preparation)

Friedrich, E. V. C., **Zillekens, I. C.**, Biel, A. L., Sauseng, P. & Schilbach, L. (2019). EEG correlates of the perception of communicative point-light stimuli. (Manuscript in preparation)