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Cerebral activation patterns and functional connectivity during perception of social cues in people with autism spectrum disorder and typically developed controls - an fMRI study

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Meinen Eltern und Großeltern

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List of abbreviations

A	-	Anterior
ACC	-	anterior cingulate cortex
AQ	-	autism quotient, a questionnaire exploring the severity of autistic traits
ar/prMFC	-	anterior rostral/posterior rostral medial prefrontal cortex
ASD	-	autism spectrum disorder
BOLD-signal	-	blood oxygenation level dependent level
CSL	-	complex social laughter (socially including or excluding laughter)
D	-	Dorsal
DSM-V	-	diagnostic and statistical manual of mental disorders, fifth edition
EVA	-	emotional voice area
FFA	-	fusiform face area
FFG	-	fusiform gyrus, a region involved in the processing of human faces
fMRI	-	functional magnetic resonance imaging
ICD-10	-	International Statistical Classification of Diseases and Health Related Problems
ICQ	-	Interpersonal Competence Questionnaire
IFC	-	inferior frontal cortex
IFG	-	inferior frontal gyrus
JOY	-	socially including (e.g. joyful) laughter
LSAS	-	Liebowitz Social Anxiety Scale
LSAS-A	-	Liebowitz Social Anxiety Scale, markedness of anxiety
LSAS-V	-	Liebowitz Social Anxiety Scale, markedness of avoidance
MFC	-	medial frontal cortex
MOG	-	middle occipital gyrus
MSCEIT	-	Mayer-Salovey-Caruso Emotional Intelligence Test
MVPFC	-	medial ventral prefrontal cortex
OFC	-	orbito-frontal cortex
Ol	-	orbitolateral
P	-	posterior
PhoPhiKat	-	Test screening for gelotophobia, gelotophilia, and katagelasticism
PPI	-	psycho-physiological interaction
R	-	rostral
SCID	-	Structured Clinical Interview for DSM-IV
SMA	-	supplementary motor area
SREIT	-	Self Report Emotional Intelligence Test
STG	-	superior temporal gyrus
STS	-	superior temporal sulcus
TAU	-	socially excluding (e.g. taunting) laughter
TD	-	typically developed (controls)
TIC	-	tickling laughter
ToM	-	Theory of Mind
TPJ	-	temporo-parietal junction
TVA	-	temporal voice area
WAIS	-	Wechsler Adult Intelligence Scale

1. Introduction

1.1. Overview

In 1872, Charles Darwin published his book „The Expression of the Emotions in Man and Animals“, exploring the origin and nature of human emotions (Darwin et al., 1999). In this publication, he addressed the purpose emotions serve in communication and drew parallels between facial expressions in humans and animals. He pointed out similarities in the non-verbal communication of social signals between apes and humans, focusing, among others, on a particular social cue - laughter.

As Darwin had shown, emotions can be conveyed through different social cues and play a crucial role in communicating with others. Furthermore, research has found that they help us in mentalizing tasks, i.e. deducing the emotional and mental states of the people around us and serve many purposes, such as action-planning, behavior congruent with social norms, and action and reward anticipation (Adolphs, 2001; Amodio et al., 2006; Niedenthal et al., 2012).

The importance of being able to „read“ the emotions of others and to deduce their possible mental states also becomes evident in several psychological disorders (like mood disorders, bipolar disorder, autism, and schizophrenia (Hofer et al., 2010; Townsend et al., 2012; Vaskinn et al., 2013; Hoertnagl et al., 2014)), in which social cognitive processes can be impaired. Affected persons exhibit problems in interpersonal interaction, have difficulties interpreting facial expressions of others, and often struggle to identify social conventions and to act according to them. Also, similar behavioral differences can be observed in cases in which lesions, e.g. in stroke or multiple sclerosis, caused damage to specific brain areas (Adolphs et al., 1994; Scott et al., 1997; Sato et al., 2002). Among other techniques, functional imaging has played a significant role in the study of these cases of brain lesions and of neuropsychiatric disorders, providing valuable insight into the neural correlates of conditions presenting themselves with difficulties in social interaction. Furthermore, it helped to understand the processing of emotional cues in the unaffected brain and identify nodes and networks involved in social cognitive processes. Nevertheless, many neural mechanisms of psychiatric conditions and networks involved in emotion perception and processing are the focus of current research and remain yet to be fully understood.

This introduction is aimed at providing a brief theoretical background for the following study. First, it presents an overview of the theory regarding emotions, of the characteristics of emotional cues in general, and, in more detail, of laughter. The concepts of social perception and theory of mind, as well as their neurological correlates are being shortly reviewed and the neural mechanisms of laughter perception are being discussed in this context. The second part focuses on social perception in autism spectrum disorder. Characteristics and diagnostic criteria of ASD are being explained, followed by a paragraph discussing current research on social perception and possible neural correlates in this disorder. At last, the aims and hypotheses of the study are being formulated against this background.

1.1.1. The circumplex model of emotions

In the past, several models concerning the concept of emotion have been put forward, focusing on the dimensional aspect of emotion perception. One of these models is the circumplex model by Russell (J.A. Russell, 1980), in which he proposes that different emotional states can be described by two neurophysiological factors - i.e. by their respective valence and arousal (compare Fig. 1). In this model, valence describes as how pleasant or unpleasant a certain emotion is being perceived. Arousal on the other hand relates to the degree to which an emotion causes alertness (boredom for example being associated with little arousal, and nervousness with high arousal).

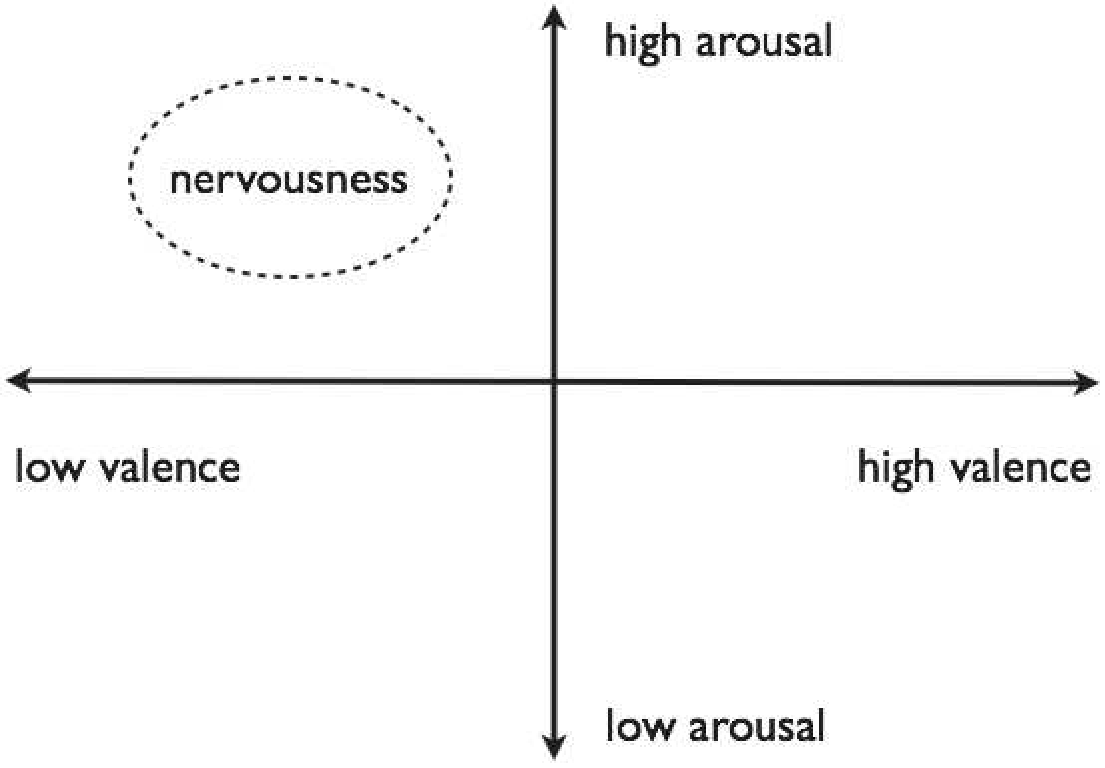

Figure 1. Circumplex dimensional model of emotion after Russell et al. (1980). In the model proposed by Russell et al., each emotion can be characterized by its valence and the arousal associated with it. Here, nervousness, as an emotion characterized by low valence and high arousal, is given as an example. (Diagram adapted after Russell et al., 1980).

1.1.2. Characteristics of emotional signals

There are several different modalities through which emotional cues and social signals can be conveyed. Of course, emotions and feelings can be expressed verbally, communicating an inner state by putting it into words. But emotions can also be conveyed non-verbally. For example, apart from *what* is said, the way *how* something is said reveals important information about how the speaker feels. This prosody - the intonation and stress put on syllables, the volume, pitch and rhythm used - can communicate important information about the speaker‘s emotional state or intentions and can even add to or alter the literal meaning of the words spoken (Mullennix et al., 2002; Nygaard et al., 2002; Nygaard et al., 2008; Cole, 2015). For example, raising the voice at the end of a sentence can be used to indicate a question. Likewise, social cues can be imparted by non-verbal communication relying on visual signals. Facial expressions can convey widely understandable emotional cues (e.g. a fearful facial expression), but also more complex communicative information. Depending on which muscles are activated, a smile can be perceived as friendly and genuine (sometimes called a „Duchenne smile“, involving the orbicularis oculi muscles as well as the zygomatic muscles (Ekman et al., 1990)) or as expressing more negative feelings (when the ocular muscles are not involved (Surakka et al., 1998)). Recent research has also shown that in deducing another person‘s mental state, observers rely more on non-verbal than on verbal signals (Jacob et al., 2012; Jacob et al., 2014), especially when both modalities carry contradictory information. In this case, non-verbal signals tend to be received as being more authentic and more reliable for judging the other‘s actual mental state (Jacob et al., 2012).

In addition to and together with facial expressions, body language in a broader term - such as gait, posture, and gestures - serves as a mean of social communication (de Gelder, 2006; de Gelder et al., 2015; Suslow et al., 2015; Martinez et al., 2016). It can be used either as a nonverbal intentional communicative signal (like pointing, beckoning, gaze direction (Black, 2011)), non-intentional conveyer of information (indicating, for example, self-confidence or fear (de Gelder et al., 2004)), or for underlining verbal information. Gestures tend to be influenced by cultural background and need to be learned; in fact, there is evidence that it is vital to apprehend and employ language-specific non-verbal communication signals in order to learn a foreign language comprehensively (Pennycook, 1985; Kellerman, 1992; Black, 2011).

In addition, there are also non-verbal vocal signals, that are ubiquitous in human communication (like sighs and laughter, for example). Laughter is an interesting social cue to study in this context, as it is a non-verbal multimodal stimulus combining an auditory modality (that also exhibits prosody) with a visual modality, i.e. facial expression, aiding interpretation.

1.1.3. Laughter as an emotional signal

Laughter is a social cue that is not limited to humans but that can also be observed in apes and other mammals such as rodents (Davila Ross et al., 2009; Leavens et al., 2016). Especially tickling laughter, which has a reflex-like character as it is elicited by touch and body contact, seems to be a phylogenetic old behavior (van Hooff, 1972; Panksepp et al., 2003). Panksepp et al. showed that rats emit very high frequency sounds when tickled by humans or touched by a conspecific (Panksepp et al., 2003; Panksepp, 2007). Studies have shown that tickling laughter is exhibited in game and playing situations, thus serving an important role in group formation and perpetuation of social relationships [1] (Davila Ross et al., 2009; Provine, 2013). In humans, tickling laughter is often observed in interaction between children and their parents, strengthening their close relationship, and between children playing (Provine, 2004). Here, tickling laughter is thought to serve play-like learning of how to protect body parts that are potentially vulnerable - like the belly or the neck, which are especially ticklish (Alexander, 1986; Weisfeld, 1993). There is evidence that susceptibility to tickling might be decreasing with age (Weisfeld, 1993; Rygula et al., 2012).

But the range of human laughter has evolved beyond tickling laughter and its involuntary, reflex elicitation. Humans also use complex social laughter - a variety of laughter types that can convey many different emotional states, like joy or mocking somebody. These laughter types differ in acoustic presentation and also exhibit prosodic characteristics (Szameitat, Alter, Szameitat, Darwin, et al., 2009; Szameitat, Alter, Szameitat, Wildgruber, et al., 2009) - tickling laughter, for example, is characterized by a high frequency as well as short and frequent laughter bouts.

Although joyful laughter occurs in „funny“ situations - the comedy arising from incongruity, e.g. a potentially „dangerous“ situation that is ridiculed and proven not to be „dangerous“ at all (the so-called false-alarm theory (Ramachandran, 1998)) - complex social laughter is used as a communicative tool and not

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[1] In studies with apes, laughter functioned as a way of distinguishing between „us“ and „others“, resolvement of fights in hierachy and in avoiding conflicts (Eibl-Eibesfeldt, 1970; Szameitat, Alter, Szameitat, Darwin, et al., 2009).

seldom deliberately. A number of studies have shown that most often it is the speaker who laughs, not the listener, that it is not about jokes we laugh most (Provine, 2004; Vettin et al., 2004), and that we tend to laugh much more in company (up to five times during ten minutes (Vettin et al., 2004; Provine, 2013)). In the light of these findings, it is interesting to investigate how laughter as a non-verbal social signal is perceived and processed at the neural level.

1.1.4. The social perception network

Neuroimaging studies have identified several brain regions that are activated in response to social and emotional stimuli. Together, these regions are forming different networks that are involved in social cognition - serving Theory of Mind, empathy, action observation, social and emotion perception, and social behavior (Yang et al., 2015; Henry et al., 2016). Two of these networks - the social perception network and the network serving theory of mind - shall be described here in more detail.

The social perception network consists of several regions subserving the perception of human faces and voices - most notably the fusiform face area, the temporal voice area, the posterior superior temporal sulcus, and the amygdala (Henry et al., 2016, also compare Figure 2).

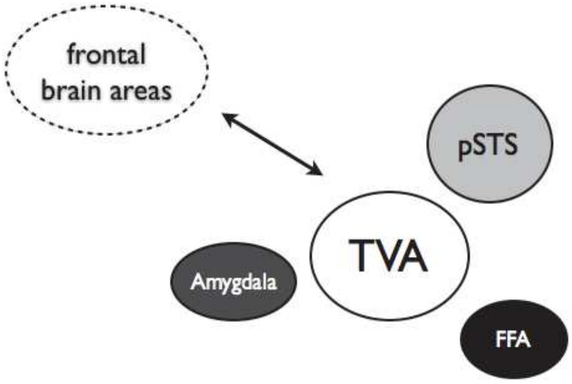

Figure 2. Nodes of the social perception network. The most important regions involved in integrating social stimuli - temporal voice area (TVA) and posterior superior temporal sulcus (pSTS) for human voices, fusiform face area (FFA) for faces and the amygdala for attributing valence. Frontal brain areas are involved in higher integrative processes. (Figure adapted according to a review by Henry et al. (2016)).

According to the model of Haxby et al., the regions involved in the perception of human faces can be divided in a „core“ network and an „extended“ network, both of which are bilateral (compare Figure 3). The core network, which incorporates parts of the extrastriate visual cortex, is employed to identify constant characteristics of faces (a process involving activation in the fusiform and the inferior occipital gyrus) and variable features like gaze direction (which elicit activation in the posterior superior temporal sulcus (Haxby et al., 2000; Hoffman et al., 2000; Haxby et al., 2002)). The more extended facial recognition network serves cognitive functions which help to ascribe an affective meaning to the faces perceived (Haxby et al., 2000; Duchaine, 2015). It includes the amygdala, the insula, the orbitofrontal cortex, and the inferior frontal gyrus. The insula seems to be associated with the analysis of facial expression (Phillips et al., 1997; Chen et al., 2009). The activation in the orbitofrontal cortex apparently is related to judging facial attractiveness, while the inferior frontal gyrus is involved in providing semantic information (Poldrack et al., 1999; O'Doherty et al., 2003). And the amygdala, an important node in many cognitive processes, contributes in attributing affective salience to faces and facial expressions and thus in identifying possibly threatening situations (Gallagher et al., 1996; Phelps et al., 2005; LeDoux, 2007).

The perception of human voices activates a region in the bilateral superior temporal sulcus and gyrus, known as the temporal voice area (Belin et al., 2000). In this region, hemodynamic responses to human voices are increased as compared to the responses to either animal sounds or environmental noise. Furthermore, a specific area within the TVA, the emotional voice area (EVA), has been identified to be sensitive to emotional prosody. This area is exhibiting structural connections with the ipsilateral medial geniculate body. Furthermore, Ethofer et al. found structural connections between the EVA and frontal brain areas, more specifically the ipsilateral inferior frontal gyrus (IFG, which also exhibited a functional connectivity with the EVA) and the inferior parietal lobe (Ethofer et al., 2012; Ethofer et al., 2013).

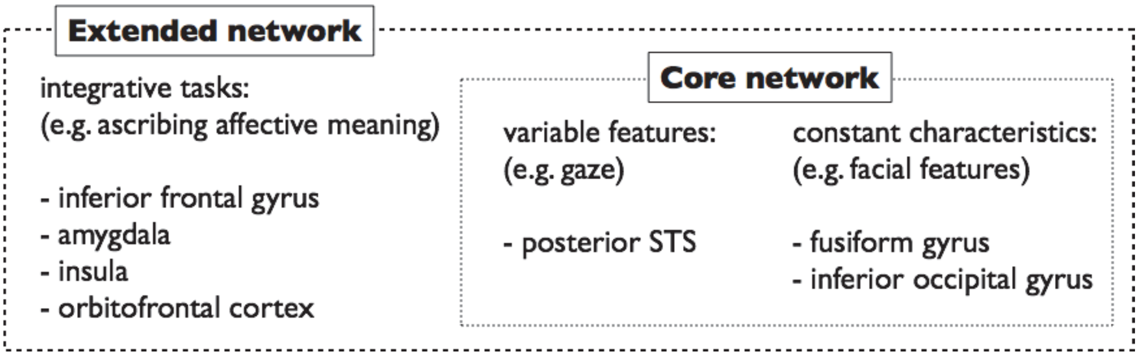

Figure 3. Areas involved in the perception of human faces. According to Haxby et al., a core network and an extended network are involved in the perception and integration of human faces (Haxby et al., 2000, 2002). The regions of the core network are associated with the perception of constant and variable characteristics of human faces, while the nodes of the extended network are related to higher integrative processes.

Apart from the temporal voice areas, and also presumably forming a more extended network, the amygdala and the inferior frontal gyrus are associated with the processing of human voices as recent research has found (Belin et al., 2004; Pernet et al., 2015). Considering integration of nonverbal cues from voice and face, an area in the right pSTS has been identified to subserve integration of simultaneously presented signals from human voices and faces (Watson et al., 2014).

In addition to the mere identification of human voices the processing of prosody is very important for social communication, as it carries affective and linguistic information (Brueck et al., 2011,Wildgruber et al., 2006). Different brain regions and structures, both cortical and sub-cortical, are related to prosody processing, depending on whether linguistic or affective prosody is presented and whether or not attention is paid to prosody explicitly (Wildgruber et al., 2004; Fruhholz et al., 2012). Explicit appraisal of linguistic prosody is associated with areas of speech processing in the left hemisphere, while explicit assessment of affective prosody elicits an increase in BOLD-signals in the right posterior STS, the bilateral orbitofrontal cortex, and the inferior frontal gyrus as compared to implicit evaluation of prosody ((Bruck et al., 2011, Pihan, 2006; Wildgruber et al., 2006; Wildgruber, Ethofer, Grandjean, Kreifelts, 2009).[2]

Taking into account recent fMRI studies, Bruck et al. propose a network model encompassing the different structures contributing to the processing of prosodic information (Bruck et al., 2011). They underline the importance of the primary auditory cortex and the rpSTC and bilateral DLPFC and OFC in the explicit processing of prosody. The rpSTC also seems to serve as an integration area for prosodic information and visual (facial) cues, contributed by the primary visual cortex and the FFA. The amygdala and the arMFC on the other hand play a role in the implicit processing of prosodic information (Bruck et al., 2011, also Figure 4). The authors point out that the regions like limbic structures and the basal ganglia are also thought to contribute to this network, although their role seems much less clear.

So although there are many more regions sub-serving and contributing to cognitive processes in the perception of human faces and voices, the fusiform face areas, the TVA, the pSTS as well as the amygdala and the OFC are consistently activated by social cues and can thus be thought of as central nodes of the social perception network (Yang et al., 2015; Henry et al., 2016).

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[2] The OFC has been associated with explicit appraisal of emotions (Rolls, 1996) while the IFG has been found to play an important role in working memory. It also displays high hemodynamic response during go/no-go tasks, implicating an involvement in decision making (Aron et al., 2004; Chikazoe et al., 2007; Hampshire et al., 2010).

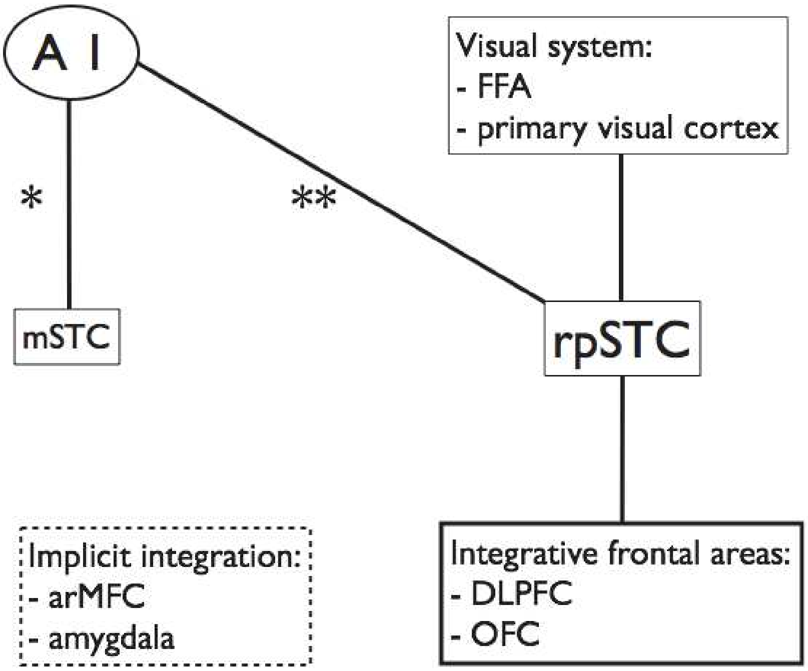

Figure 4. Network model for prosody perception and integration. The connection between the primary auditory cortex (A 1) and the mid-superior temporal cortex (mSTC), marked *, is stimulus-driven and not limited to prosody perception. The connection between A1 and the right posterior superior temporal cortex (marked **), is task driven and associated with explicit prosody evaluation. The rpSTC also receives input from visual areas (FFA - fusiform face area). The orbitofrontal (OFC) and dorso-lateral prefrontal cortex (OFC) are associated with higher integrative and mentalizing tasks. Areas involved in the implicit processing of prosody involve the anterior rostral medial frontal cortex (arMFC) and the amygdala. (Figure adapted from Bruck et al, 2011).

1.1.5. Theory of mind

But in order to understand what these emotional and social signals tell about another person, their thoughts and intentions, the recipient has to be able to infer the probable emotional state of the person exhibiting emotional cues - an ability known as mentalizing or Theory of Mind (ToM). It describes the capacity to understand that other persons have beliefs, thoughts and intentions different from one‘s own, to take on their perspective, to infer what they might be thinking or feeling, and in which way this might influence their actions (Premack et al., 1978; Frith et al., 2005).

The capacity for Theory of Mind is impaired in several psychiatric conditions, contributing to the symptoms observed in these disorders. It can occur, most notably, in schizophrenia (Henry et al., 2016) and in autism spectrum disorder (ASD) (Baron-Cohen et al., 1985). The degree to which ToM impairment is found in ASD is variable - it is most often found in children and less frequently in adults, possibly reflecting a developmental delay in the ability of attributing mental states to others. Most adults with Asperger syndrome perform well on first order false belief tasks but exhibit problems with second order false-belief tasks[3] and with identifying faux-pas situations (Stone et al., 1998).

While ToM is not directly involved in the perception and processing of emotional stimuli, it is a prerequisite for their interpretation, i.e. for understanding the causes of emotional and social signals as well as the feelings, beliefs and possible future actions of the person communicating them. This, in turn, is important for interacting with others and for guiding our own behavior in groups and social interaction in general.

1.1.6. Perception and processing of laughter

Although several studies have examined the perception of laughter as compared to other affective stimuli (Sander et al., 2001, 2005), only few have focused on how different types of laughter are processed by the brain (Szameitat et al., 2010; Wildgruber et al., 2013; Kreifelts et al., 2014). And yet, the distinction between tickling laughter and complex social laughter types - regarding elicitation, physical characteristics, and situations in which it is employed - also hold true for the neural correlates of laughter perception, as has been demonstrated by Szameitat et al. (Szameitat et al., 2010). They showed that tickling laughter, which has a high frequency of laughter bouts and a high acoustic complexity, primarily causes BOLD-signal changes in the right mid-posterior STG, more specifically the above-mentioned emotional voice area within the TVA, when compared to other complex social laughter types (Szameitat et al., 2010; Ethofer et al., 2012). This region is also involved in

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[3] False-belief tasks are used to examine theoy of mind concepts as they test the ability to make inferences about other people‘s mental states. First-order false belief describes the ability to understand a false assumption another person has of a real situation whereas second-order false belief describes the ability to infer what a person might think about a second person‘s thoughts (Wimmer et al., 1983; Perner, 1985).

analyzing acoustic characteristics and has been shown to be activated by affective auditory stimuli (Leitman et al., 2010), pointing towards an analysis mainly of the auditory characteristics of this laughter type. The complex social laughter types of joyful and taunting laughter, however, gave rise to an activation in the arMFC - a key node of ToM processes, i.e. the inference of others‘ mental states (Amodio et al., 2006). Intriguingly, the authors were able to show that this arMFC activation was present in both explicit and implicit affective evaluation, without a difference between the two CSL types (Szameitat et al., 2010). During the explicit affective evaluation of laughter, they also found activity in the right posterior STS and in the bilateral orbitolateral IFG and prMFC. This set of regions is reflecting the different processes necessary for assessing affective content of auditory cues - the rpSTS is associated with the perception of emotional speech prosody, the MFC is activated in tasks that require the focusing of attention and monitoring of actions, and the IFG plays a role in working memory, attention, and the evaluation of linguistic prosody (Rama et al., 2001; Amodio et al., 2006; Wildgruber et al., 2006; Leitman et al., 2010).

Wildgruber et al. investigated connectivity between regions involved in the processing of laughter using a PPI-analysis (Wildgruber et al., 2013). The authors report an increased connectivity between regions within the auditory association cortex as well as between the auditory association cortex and prefrontal brain areas (namely the pdIFG, olIFG, and prMFC) during the perception of tickling laughter. Furthermore, an increased connectivity of the right mSTG and right pdIFG with the SMA was observed. In response to taunting laughter, connectivity was increased between the TVA and the arMFC. According to the authors, this increased connectivity could be the correlate of an automatic mentalizing process, needed to reliably identify possible negative intentions of the person laughing.

The perception of joyful laughter, on the other hand, was associated with an increase in connectivity between the TVA and visual regions. This increased connectivity could be the neurobiological correlate of an association between the perception of joyful laughter and visual memories - like those of friendly facial expressions (Wildgruber et al., 2013). These findings show that the perception of different types of social laughter is associated with increases in connectivity between auditory areas and other brain regions, which differ, depending on which type of laughter is perceived. This might point towards different cognitive processes taking place during the perception of social laughter types.

1.1.7. Emotions and mental disorders

There are several psychiatric conditions which are associated with difficulties in perceiving, analyzing, and interpreting social and emotional signals. Given the importance of correctly interpreting social cues and to act accordingly, these difficulties may cause severe distress for those affected. As the neural correlates underlying these impediments, however, are often not well-understood, there is need for research in order to identify causes and better understand key mechanisms of these conditions.

1.2. Autism Spectrum Disorder

1.2.1. Definition and diagnostic criteria

Autism spectrum disorder is characterized as a neurodevelopmental disorder that presents itself with stereotyped behavior, a focus on details or specific items, and, most strikingly, difficulties in social interaction. It was described in 1938 by Asperger and 1943 by Kanner (Kanner, 1968; Chown et al., 2016).

For a diagnosis of childhood autism (F.84.0) according to the ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th edition), the following criteria must be met:

A) Developmental deficits or differences that are manifest at an age younger than three years old. These differences can present themselves in the use of language in social interaction and in the development of relationships to others. Also, the ability for imaginative play („as if“) is often lacking.

B) Differences in the reciprocity of social contact. This involves inadequate non-verbal communication (like avoiding eye-contact) and difficulties in understanding and relating to another person‘s emotions. Behavior can seem unsuited for a particular social situations or to social norms. Affected persons have difficulties in developing age-appropriate peer relationships and in sharing mutual interests with others.

C) Communicational difficulties. Speech development is often delayed or lacking and initiating a conversation is difficult. Speech prosody can be differing while words or parts of sentences are repeated or employed in a stereotyped manner.

D) Stereotyped behavior and narrow range of interests. This can present itself in peculiar interests, in focusing on a part or certain aspect of an object, or in an unusual intensity, with which an interest is pursued. Routines are followed meticulously and even small changes in these routines or in the familiar environment cause distress. Repetitive and stereotypical moves can also be present.

E) The clinical presentation could not be explained better by another developmental disorder.

The diagnostic criteria for Asperger‘s syndrome (F84.5) are similar to those for childhood autism:

- People with Asperger‘s syndrome exhibit the same difficulties in social interaction as people with childhood autism.
- In Asperger‘s syndrome, repetitive behavior and special interests are also present. However, repetitive movements and focus towards parts of an object are less frequent.
- The main difference in diagnostic criteria between Asperger‘s syndrome and childhood autism is the absence of a developmental delay regarding language and cognitive abilities. There may be a delay in reaching motor milestones.

Overall, ASD is a complex neurodevelopmental disorder which can present itself with a variety of symptoms. The severity of these symptoms can range from mild and hardly affecting everyday-life to very pronounced deficits in social interaction and severe impairments, e.g. in an occupational context.

1.2.2. Emotion recognition and processing in ASD

Which neural processes might underlie the symptoms outlined above is the focus of intensive research. [4]„In the search for these neural correlates, studying key brain areas involved in the perception and processing of social stimuli such as faces or voices might provide answers. Current models of face and voice processing suggest that in this context a set of brain regions including the amygdalae, the posterior temporal cortex (pSTC), the fusiform gyri, the occipital face area (OFC), and the temporal voice areas (TVA) might be of particular interest (Haxby et al., 1996; Belin et al., 2000; Haxby et al., 2002; Kreifelts et al., 2007; Wildgruber et al., 2009; Bruck et al., 2011; Ethofer et al., 2012).

Indeed, a number of studies suggest that difficulties observed in the interpretation of social signals in autism may be associated with differences in the activation of several of these areas involved in the processing of facial and vocal cues (Critchley et al., 2000; Dalton et al., 2005; Watanabe et al., 2012). With respect to the processing of facial signals, for example, several studies consistently found a hypoactivation in brain regions involved in the processing of basic facial features, particularly the FFA, as well as brain regions involved in higher order processing such as the medio-frontal cortex (Hubl et al., 2003; Dalton et al., 2005). Studies on the processing of auditory social signals such as prosody or laughter present evidence of hypoactivation in brain-regions involved in the processing of basic vocal features in ASD patients (Gervais et al., 2004; Wang et al., 2006; Eigsti et al., 2012).

However, some authors propose that alterations in connectivity might be an even more important correlate of behavioral deficits in ASD (Belmonte, Cook, et al., 2004; Welchew et al., 2005). Studies investigating brain connections consistently present evidence on ASD-related alterations of brain connectivity, including a long-range hypoconnectivity and short-range hyperconnectivity (Castelli et al., 2002; Belmonte, Allen, et al., 2004; Courchesne et al., 2005, Di Martino et al., 2014, Ameis et al., 2015, Hernandez et al., 2015).

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[4] All following paragraphs that are highlighted with underscore and indicated with quotation marks have been cited verbatim from (Hoffmann et al., 2016). Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Journal of Neural Transmission, 123(8), 937-947. Reduced functional connectivity to the frontal cortex during processing of social cues in autism spectrum disorder. Hoffmann, E., Bruck, C., Kreifelts, B., Ethofer, T., & Wildgruber, D. Springer Vienna (2016). https://link.springer.com/journal/702

Still, neither alterations of connectivity nor hypoactivation alone may suffice to explain difficulties in social perception in ASD. Recent studies argue against a monocausal explanation and rather advocate a more complex one including both a hypoactivation and a reduction in connectivity in ASD at the same time (Minshew et al., 2010; Sato et al., 2012).“

Recently, yet another hypothesis has been put forward by Hahamy and colleagues (Hahamy et al., 2015), trying to reconcile those inconsistent and apparently contradictory findings. The authors provide evidence for a high idiosyncrasy in the brains of ASD individuals - i.e. the fact that changes in connectivity exhibited a high variability between subjects, but were constant for each individual. Furthermore, the extent of changes in connectivity were correlated with the severity of ASD, as determined in behavioral tests. Taken together, the highly individual connectivity patterns could result in a „regression to the mean“ when averaging data sets (Hahamy et al., 2015), providing a possible explanation for seemingly conflicting study results.

1.2.3. Laughter recognition and processing in ASD

Although a lot of research has focused on the perception and processing of different social cues and ToM in ASD, laughter and humor in ASD have scarcely been studied. Of those studies addressing this subject, most are observational or behavioral studies in children with ASD, often focusing on humor rather than CSL.

Studies have shown that individuals with autism tend to laugh less and in different situations compared to TD controls, i.e. they often laugh when alone or in situations where nobody else laughs, and they do not laugh reciprocally (St James et al., 1994; Reddy et al., 2002). Children with ASD also exhibit a restricted affect when presented with laughter (Helt et al., 2016). In comparison with TD children, they only show one type of laughter (Hudenko et al., 2009), possibly to communicate a positive affect and not using it as a tool in social interaction. Interestingly, laughter by ASD children is preferred by listeners rather than the laughter of TD children (Hudenko et al., 2012), although no group difference was found regarding acoustic properties (Hudenko et al., 2009). Although ASD individuals have a sense of humor (St James et al., 1994; Lyons et al., 2004), they often have problems understanding cartoons and complicated jokes requiring ToM (Emerich et al., 2003) - yet there are some case reports of highly developed humor in (female) ASD individuals (Lyons et al., 2004). There are many explanations as to what might contribute to the altered comprehension of humor in ASD: ToM deficits (which are present even in ASD individuals with a high IQ), problems in communication, difficulties in abstracting from the present context or literal meaning of a word, and, possibly, an impairment in episodic memory (Lyons et al., 2004). A study by Samson et al. (Samson et al., 2011) has shown higher scores of gelotophobia and a reduced gelotophilia in people with ASD. How joyful and taunting laughter is perceived by ASD subjects on a neural level, however, has not been studied so far.

1.3. Aims and focus of the study

The present fMRI study comparing ASD subjects and TD controls was divided into two parts aimed at investigating 1) the implicit processing of social cues and 2) the perception and processing of tickling and CSL types during a ToM task. In both experimental set-ups, we sought to evaluate differences in behavioral data between groups and ASD-related changes in the activation of key brain regions involved in the processing of facial and vocal cues. Therefore, the data sets of both experiments were analyzed for hemodynamic changes and for differences in activation between groups. Following the activation analysis, a connectivity analysis was conducted, using a psychophysiological interaction approach. Likewise, results were tested for group differences. In addition to the experiments conducted in the scanner, participants were asked to complete several questionnaires.

In the analysis of questionnaires, we expected to find a marked gelotophobia in the ASD group with low scores for gelotophilia but no group difference for katagelasticism, as found by previous studies (Samson et al., 2011). We also hypothesized to find a more pronounced social anxiety and higher depression scores in the ASD group, as insecurity in social interaction and depressive symptoms are common in ASD (*Diagnostic and Statistical Manual of Mental Disorders* 2013). The interpersonal competence questionnaire (ICQ) and the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) were conducted as an explorative approach to test for differences between the two groups.

The first fMRI experiment, consisting of three different experimental set-ups, was aimed at identifying regions sensitive to human faces, voices, and areas involved in the integration of audiovisual stimuli. The hemodynamic responses elicited by these stimuli - in both groups taken together - were used to define regions of interest (ROI). No explicit instruction to pay attention to emotional stimuli was given beforehand.

„Based on current models of face and voice processing (Haxby et al., 2000, 2002; Belin et al., 2004; Kreifelts et al., 2007; Pernet et al., 2015)“, we expected to find strong and consistent activation in areas of the social perception network, so emphasis was laid on the following brain regions: The amygdalae and the fusiform gyri as face-processing areas, both mid-superior temporal cortices as voice-processing regions, and posterior areas of the superior temporal cortex involved in the audiovisual integration of facial and vocal information. Based on evidence of ToM deficits in ASD (Baron-Cohen, 1995; Rutherford et al., 2002; Pelphrey et al., 2011), we cautiously hypothesized to find a reduction in connectivity among the regions of the social perception network as well as between these regions and frontal brain regions involved in higher-order cognitive integration - especially as in this experimental set-up, emotional cues were perceived implicitly.

In the second fMRI experiment, we investigated how laughter is perceived and interpreted by individuals with ASD using audio-visual stimuli of three different types of laughter and a mentalizing task using two different explicit instructions - the participants were asked to imagine either being the focus or the observant of laughter. Behavioral data was recorded as participants were asked to rate the valence of the individual laughter types.

As gelotophobia has been reported in ASD (Samson et al., 2011), we assumed to find a negative bias towards all laughter types in the ASD group; i.e. a disparity in the behavioral data between the two groups, with the ASD group tending to interpret laughter overall as more aversive and hence to exhibit lower ratings than TD controls. We tentatively assumed that ASD individuals might have difficulties in differentiating between the individual laughter types. Therefore, we expected that differences between groups in ratings of individual laughter types would be more pronounced for the rating of laughter with a positive valence, as ASD subjects were expected to rate this type of laughter more negatively and to be more likely to confound it with laughter with a negative valence. Likewise, we expected to find a less pronounced difference between groups in rating laughter with a negative valence, as here, the negative bias of ASD individuals towards laughter would have less impact on the already expected low valence ratings. Therefore, we also assumed to find smaller differences in ratings when comparing tickling laughter and the individual CSL types (e.g. comparing the valence ratings of JOY with TAU) in the ASD group as compared to TD controls.

Based on findings of ToM deficits in ASD (Baron-Cohen, 1995), which might result in problems with taking on the perspective of an uninvolved observer of laughter, we assumed to find decreased task-dependent differences in valence ratings in ASD subjects as compared to TD controls - e.g. a smaller difference in laughter ratings in the ASD group between a situation where subjects were asked to rate the laughter while imagining themselves as the addressee of laughter (SELF perspective), and a situation where they were asked to rate the laughter while taking on the perspective of an observer seeing another person laughing (OTHER perspective).

In an explorative approach, reaction time was also analyzed and tested for differences between groups. Here, we expected to find longer reaction times in ASD individuals, as deficits in perception and interpretation of social signals are important diagnostic criteria in ASD and might be related to slower processing of emotional cues.

In the second fMRI image analysis, we expected to find activation in response to all laughter types in the nodes of the social perception network - i.e. in the ROI that were defined using the activation patterns in the audio-visual social perception experiment. Based on the findings of previous studies which found hypoactivation in important nodes of the social perception network (like the FFA and the amygdala (Hubl et al., 2003; Dalton et al., 2005, H. Gervais et al., 2004; Wang et al., 2006; Eigsti et al., 2012)) in ASD and in analogy with the expected differences in ratings, we hypothesized that activation in these nodes in response to laughter in general would be smaller in the ASD group than in the TD control group. In analogy to the expected behavioral differences between both groups in the rating of laughter when taking on different observer perspectives (i.e. imagining being the addressee of laughter or being an observer seeing another person unrelated to them laughing), perspective-task related differences in activation between both groups were also investigated. Here, we expected to find differences in activation in regions that are involved in theory of mind tasks, like the arMFC (Amodio, 2006) and the precuneus (Cavanna et al., 2006). In a more explorative approach, we tested for differences in activation patterns in response to distinct laughter types, when contrasted with each other (e.g. taunting laughter vs. joyful laughter). We based this tentative hypothesis, i.e. finding activation differences between groups when contrasting laughter types, on the above-mentioned assumption that ASD individuals would show smaller differences in ratings between the individual laughter types.

In the connectivity analysis, we assumed to find a reduction in connectivity between areas of the social perception network and between those areas and frontal brain regions involved in mentalizing processes in the ASD groups in response to laughter in general. More specifically, based on our results of the audio-visual social perception experiment, we expected to find a reduction in connectivity between the temporal voice areas and the frontal cortex. In analogy to the activation analysis, we also investigated possible changes in connectivity related to task and to differences between the types of laughter.

To our knowledge, no imaging study on the processing of complex social laughter types in ASD has been conducted up until now. By studying differences in activation and connectivity in response to different types of laughter, we hope to shed some light on the possible neural correlates of laughter perception in ASD.

2. Materials and Methods

2.1. Participants

„Thirty volunteers participated in the study: 20 typically developed controls (10 female, mean age: 26.3 a ± SD 4.2 a) and 10 ASD patients (2 female, mean age: 34.1 a ± SD 10.5 a). All participants were right-handed (Oldfield, 1971) and native speakers of German. After excluding data sets with excessive head movement (compare data analysis), participants were matched into two equal-sized groups of nine participants each (TD: 2 female, mean age 31.11 a ± SD 11.12 a; ASD: 2 female, mean age 32.22 a ± SD 9.96 a)[5]. Groups were matched with regard to age, gender, level of education, and intelligence (Table 1,“ also Table 2 for the second experiment). Data sets of TD controls that were not matched to those of ASD subjects were not regarded in the following analytical steps. „TD controls were recruited via e-mail sent to all students of the University of Tübingen and employees of the university's hospital. None of the controls reported any neurological or psychiatric illness in the past or present. To assure that none of the control participants suffered from a mental disorder, each participant was interviewed using the SCID-I based screening questionnaire (First et al., 1996; Gast et al., 2001; First et al., 2002). In order to exclude prominent autistic traits in the TD group, an abbreviated German version of the autism questionnaire (AQ) (Baron-Cohen et al., 2001) was completed by all TD participants, as the SCID-I does not cover ASD. The completion of the AQ by healthy controls also permitted a comparison of the severity of autistic traits of all participants.

All ASD subjects were recruited from a pool of patients treated at the University Hospital, Tübingen, Department of Psychiatry and Psychotherapy. Patients were diagnosed according to ICD-10 diagnostic criteria (WHO, 1992). The diagnostic procedure included an examination by two experienced clinicians, an assessment of verbal intelligence (MWT-B (Lehrl, 2005)) and several self-rating instruments, including AQ (Baron-Cohen et al., 2001), empathy quotient (EQ)

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[5] All following paragraphs that are highlighted with underscore and indicated with quotation marks have been cited verbatim from (Hoffmann et al., 2016). Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Journal of Neural Transmission, 123(8), 937-947. Reduced functional connectivity to the frontal cortex during processing of social cues in autism spectrum disorder. Hoffmann, E., Bruck, C., Kreifelts, B., Ethofer, T., & Wildgruber, D. Springer Vienna (2016). https://link.springer.com/journal/702

(Baron-Cohen et al., 2004), and systemizing quotient (SQ) (Baron-Cohen et al., 2003) as well as parental autism questionnaires (Fragebogen zur sozialen Kommunikation (FSK) (Bölte, 2000), Social Responsiveness Scale (SRS) (Constantino, 2013), and the Marburg Rating Scale for Asperger's Syndrome (MBAS) (Kamp-Becker et al., 2005). Only cognitively high functioning ASD subjects with the diagnosis Asperger-Syndrom (F 84.5) or high functioning early infantile Autism (F84.0) were included“ [6].

Table 1. Participants‘ age and scores yielded in intelligence tests

	ASD subjects	**SD**	**TD controls**	**SD**	**t-value**	**p-value**	**Cohen‘s d**
WAIS[1] (verbal) percentile	56.44	34.33	62.67	29.18	0.41	0.34	0.20
WAIS (operational) percentile	53.56	36.27	58.44	26.15	0.33	0.21	0.15
MWT-B[2] percentile	31.11	4.56	32.22	3.70	0.57	0.20	0.27
Age (in years)	32.22	9.96	31.11	11.12	-0.22	0.97	-0.11

„1 WAIS - Wechsler Adult Intelligence Scale, 2 MWT-B - Mehrfachwortschatz-Intelligenz-Test, all participants had at least successfully completed secondary school. Degrees of freedom t (16).“ https://link.springer.com/journal/702

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2.2. Ethic statement

„This study was conducted in accordance with the ethical principles proposed by the Declaration of Helsinki. The study protocol was assessed and approved by the ethics committee of the University of Tübingen. Each participant was given comprehensive information about the objectives of the study and the methods used in the study. Written informed consent prior to the study was mandatory for participation. All participants received a small pecuniary compensation for their participation and their travel expenses.“

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[6] Some of the ASD participants had received therapy and reported a medication with antidepressants.

2.3. Questionnaires

In addition to the diagnostic tests mentioned above, all participants performed a number of self-reporting questionnaires to test for social anxiety, emotional intelligence, depressive symptoms, and gelotophobia.

All participants were tested for gelotophobia (the fear of being laughed at), gelotophilia (the joy of being laughed at), and katagelasticism (the joy of laughing at others) using the PhoPhiKat-45 questionnaire (Ruch, 2009).

Social anxiety was also tested for with the Liebowitz Social Anxiety Scale (LSAS, (Heimberg et al., 1999)). Here, participants were asked how afraid they were of experiencing social situations and of performing certain tasks (e.g. writing something; LSAS-A). They were also asked to rate the extent to which they tend avoid such situations or tasks (LSAS-V). A total sum was then calculated using both scores.

A third test aimed at testing emotional intelligence was conducted (Mayer-Salovey-Caruso Emotional Intelligence Test, MSCEIT (J. D. Mayer, Salovey, P., Caruso D.R., 2002)). Four branches of emotional intelligence are being tested for in the MSCEIT: emotion perception, the facilitation of thoughts by using emotion, understanding the meaning and causes of emotion, and reflecting on and managing emotions according to situations (J. D. Mayer, & Salovey, P. , 1997).

With the Interpersonal Competence Questionnaire (ICQ), five qualities were being tested for: initiation (I), negative assertion (N), disclosure (D), emotional support (e), conflict management (c) (Buhrmester et al., 1988; Riemann, 1993).

Furthermore, subjects were tested for depressive symptoms using the self-report Beck Depression Inventory (BDI, (Beck, 1972; Hautzinger, 1994)). This questionnaire does not serve as a screening test for depression but for the severity of affective and somatic depressive symptoms.

2.4. fMRI experimental set-ups, tasks and stimulus material

2.4.1. Audio-visual social perception experiment

2.4.1.1. Experiment aimed at identifying face sensitive brain regions

„The task used to identify brain regions involved in face-processing relied on an experimental design established by previous studies (Kanwisher et al., 1997; Epstein et al., 1999)[7]. Pictures of either human faces, houses, everyday objects, or landscapes, blocked into groups of 45 pictures each from the same category, were shown to participants. There were eight blocks, two of pictures of faces, two of objects, two of landscapes and two of houses, each lasting 30s. In the intervals between blocks, a cross for gaze-fixation was presented mid-screen for 20 s. To ensure subjects were paying attention to the presented stimuli, they were instructed to perform a one-back matching task, i.e. pressing a button when a picture was repeated immediately. Each block contained two instances of immediate repetition, one in the first and one in the second half. For the matching tasks, participants were provided with a combined button-fiber optic system (Lumi-Touch, Photon Control, Burnaby, Canada) to be pushed with their right index finger.

Behavioral data was analyzed in order to evaluate possible differences between groups. In order to identify regions of interests, i.e. regions showing more activation to human faces as compared to other stimuli, four regressors were defined (faces, houses, objects, landscapes). These regressors were then used to calculate a contrast identifying face-selective regions (HOUSES > FACES, OBJECTS, LANDSCAPES).

2.4.1.2. Experiment aimed at identifying voice sensitive brain regions

To identify brain regions involved in the processing of human voices, we used the stimulus material and the experimental set-up established by Belin and colleagues (Belin et al., 2000). 24 different blocks of sounds plus 12 blocks of silence each 8 s in duration were presented to participants. Half of the sound

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[7] All following paragraphs that are highlighted with underscore and indicated with quotation marks have been cited verbatim from (Hoffmann et al., 2016). Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Journal of Neural Transmission, 123(8), 937-947. Reduced functional connectivity to the frontal cortex during processing of social cues in autism spectrum disorder. Hoffmann, E., Bruck, C., Kreifelts, B., Ethofer, T., & Wildgruber, D. Springer Vienna (2016). https://link.springer.com/journal/702

blocks presented human vocal sounds (e.g. speech, cries, laughter etc.), six environmental sounds (e.g. tires screeching, church-bells, or planes), and six blocks presented sounds produced by animals (e.g., mooing, gallops). All blocks were presented in a randomized order with the condition not to present more than two blocks of silence consecutively (Kreifelts et al., 2010). Participants were instructed to listen to the sounds with their eyes closed. In accordance with Belin et al. (Belin et al., 2000), this experiment was conducted as a passive listening task, so no behavioral data was recorded for this experiment. As a means of sound application all participants were equipped with MRI-compatible headphones (Sennheiser, Wedemark, Germany; modified). For this task, three regressors were defined for the image analysis: Human voices, environmental sounds and animal sounds. The contrast aiming at identifying voice sensitive brain regions was thus calculated as VOICES > ENVIRONMENT, ANIMALS.

2.4.1.3. Experiment aimed at identifying audiovisual integrative brain regions

Three different modalities of stimuli were presented: videos (audiovisual AV), muted videos (visual V), or sound recordings (auditory A). To attain these three modalities, audiovisual stimulus recordings were parted in audio and visual tracks and later presented as either combination (audiovisual stimulus) or separated versions (muted visual and auditory stimulus respectively) of the original recording. Recordings capture actors speaking single, three-syllable German words in a neutral angry, disgusted, frightened, happy, sad, alluring tone of voice. Facial expressions matched the respective intonation. A total number of 180 stimuli were divided into 12 blocks for each modality (A, V, and AV). Every block, lasting 8 s, consisted of five stimuli. Stimuli were both randomized across as well as within blocks. To ascertain attention towards the stimuli, subjects were instructed to identify the second stimulus presenting a male actor by pressing a button (Kreifelts et al., 2010).

Behavioral data was analyzed in order to evaluate possible differences between groups. In the following image analysis, three regressors were defined in a first step (audiovisual AV, auditory A and visual V). In order to identify brain regions responsive to unimodal stimuli, the following contrasts were calculated: AV > V and AV > A. To identify brain regions more responsive to multimodal audiovisual than to either visual or auditory stimuli, a conjunction of activation patterns in response to both kinds of unimodal stimuli (AV > A AND AV > V) was calculated applying a minimal t statistic based on a conjunction null hypothesis (Nichols et al., 2005)."

2.4.2. Laughter perception experiment

This experiment was aimed at identifying brain regions that are being activated in response to the audiovisual presentation of three different types of laughter. Furthermore, it was investigated whether participants showed differences in brain activation patterns when they were imagining different observer perspectives during stimulus presentation (i.e. when they were either imagining themselves as the addressee of laughter (SELF perspective) or imagining being a bystander observing a person laughing (OTHER perspective)). In a second analytical step, the connectivity between brain regions involved in the perception and processing of laughter was analyzed using a PPI analysis. Also, behavioral data (rating the perceived intention of the person observed laughing) was collected and tested for differences between groups, with regard to differences between laughter types and task instruction.

For this experiment, participants were presented with short video clips of people presenting different types of laughter. The stimuli were presented in two blocks. In each block, participants were presented with 60 short videos of faces of both male and female people laughing. The persons shown in the videos were actors who had recorded the laughter using a self-enactment method[8]. Three different types of laughter were presented: tickling laughter (TIC), friendly joyful laughter (JOY) and taunting laughter (TAU). Of every laughter category, twenty stimuli were presented. The order of stimulus presentation was randomized across participants. After each short clip, a four item rating scale was presented (compare example in Fig. 5). Participants were asked to rate how they had

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[8] The experimental task and stimulus material used was adapted from Dr. med. Benjamin Kreifelts, who designed, recorded, and edited the stimulus material (Kreifelts et al., 2014).

perceived the intention of the laughter. They could make a dimensional decision between the perceived inclusiveness of the laughter - i.e. the socially including or excluding intention, respectively, of the laughter presented in the videos. No item for tickling laughter was presented, so participants had to rate tickling laughter as the perceived it, either as socially including or socially excluding.[9] For rating the intention of the laughter, a combined button-fiber optic system (Lumi-Touch, Photon Control, Burnaby, Canada) with four buttons to be pushed with four fingers of the right hand was used.

In each of the two experimental blocks, participants were given a different instruction on which observer perspective they should assume while watching the videos. Participants were instructed to assume either the perspective of the addressee of the laughter in the videos (SELF condition) or of an unaffected bystander who witnesses an actor practicing different types of laughter (OTHER condition). They were asked to rate the social inclusiveness of the laughter as they perceived it while assuming the instructed point of view of the observer.

Both the orientation of the rating scale and the order in which the tasks were administered were balanced across all participants and between both groups.

2.5. MRI data acquisition

„MRI data was obtained using a 3 Tesla scanner (Siemens TRIO), equipped with a 12-channel head-coil (field map properties: number of slices: 30, slice thickness: 3.0 mm, TR: 400 ms, TE1: 5.19 ms, TE2: 7.65 ms, flip angle: 60°, no filter employed)[10]. Functional images were acquired using a BOLD-sensitive echo planar imaging sequence (30 slices, slice thickness: 4 mm thickness + 1 mm gap, Field of View (FoV) = 192 mm, voxel size 3 × 3 × 4 mm^3, TR = 1700 ms, TE = 30 ms, flip angle = 90°). For anatomical reference, high-resolution structural images of each participant were acquired by using a magnetization

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[9] As an ambiguous stimulus, it might be interpreted rather positive, i.e. as socially including, or negative, i.e. socially excluding, dependent on the markedness of gelatophobia.

[10] All following paragraphs that are highlighted with underscore and indicated with quotation marks have been cited verbatim from (Hoffmann et al., 2016). Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Journal of Neural Transmission, 123(8), 937-947. Reduced functional connectivity to the frontal cortex during processing of social cues in autism spectrum disorder. Hoffmann, E., Bruck, C., Kreifelts, B., Ethofer, T., & Wildgruber, D. Springer Vienna (2016). https://link.springer.com/journal/702

prepared rapid acquisition gradient echo (slices per slab: 176, slice thickness: 1 mm, FoV = 256 mm, TR = 2300 ms, TE = 2.96 ms).“

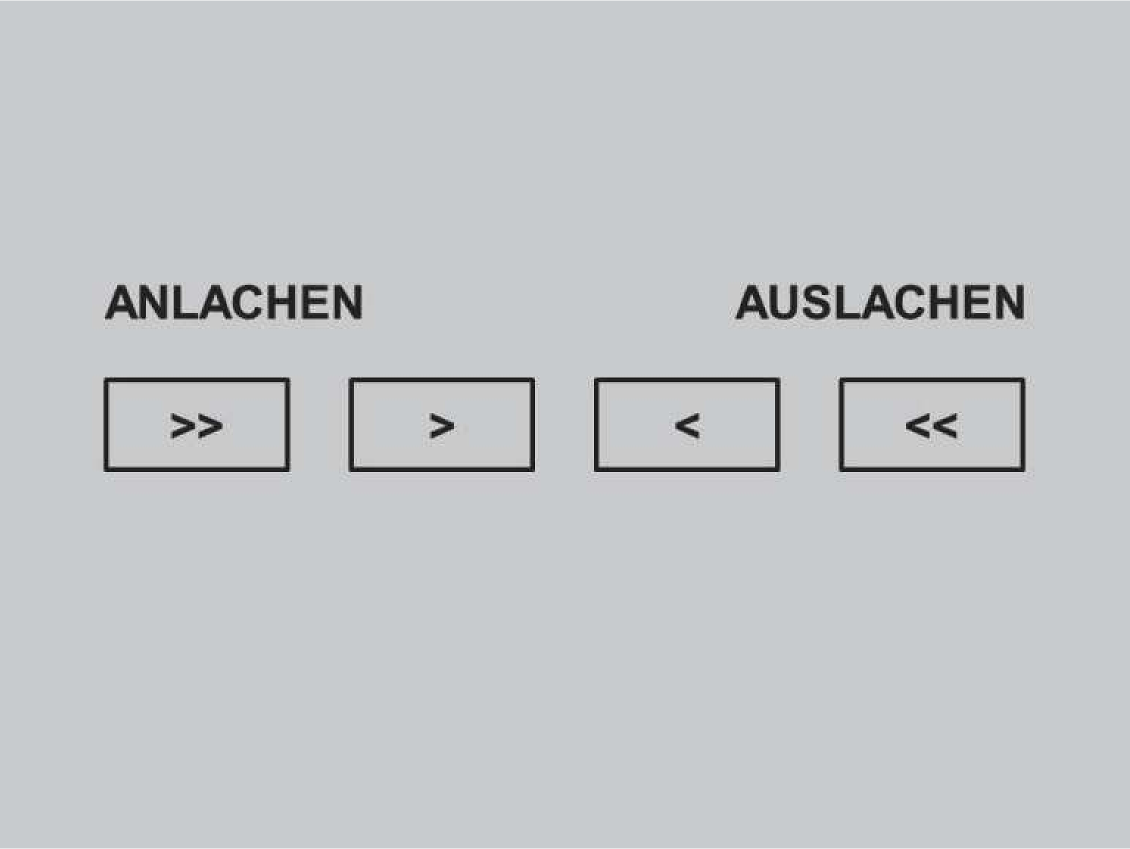

Figure 5. Four-item rating scale presented for the rating of laughter stimuli. *ANLACHEN - JOY, friendly and joyful laughter (socially including laughter), AUSLACHEN - TAU, taunting laughter (socially excluding laughter), >> - distinctively socially including character of laughter, > - rather including laughter, < - rather socially excluding character of laughter, << - distinctively excluding laughter; the orientation of the scale was balanced across participants, with half of the participants being presented with the orientation shown above and the other half being presented with a reversed scale orientation. The rating scale was presented after each laughter stimulus (this scale was adapted from Kreifelts et al., 2014).*

2.6. Data analysis

2.6.1. Analysis of questionnaires

The test results off all five questionnaires (BDI, LSAS, MSCEIT, PhoPhiKat, ICQ) were statistically analyzed and tested for possible differences between groups using t-tests.

Test results were then investigated for consistency with the previously formulated hypotheses regarding depression scores, social anxiety, and gelotophobia.

2.6.2. Analysis of behavioral data

2.6.2.1. Audio-visual social perception experiment

„For the experimental conditions identifying face sensitive and audiovisual integrative areas, behavioral data was recorded during the experiment in the scanner[11]. For the experiment aimed at identifying voice sensitive brain areas, no behavioral data was recorded as, in accordance with previous publications that had used these stimuli, this experiment was conducted as a passive listening task. Under the experimental condition aimed at identifying face sensitive regions, participants were asked to push a button when a picture was repeated immediately. At maximum, 60 repeats could be discerned. During the audiovisual integrative experiment, the second time a male actor was presented within a block of stimuli should be identified correctly. For each track (sound, muted, video with sound), 12 correct identifications could be made. Correct answers according to the task and given within a set timeframe after stimulus presentation (face task: later than 300 ms and earlier than 2000 ms, AV task: later than 1000 ms and earlier than 2000 ms after stimulus presentation) were counted as „hits". Early or late answers (later than 2000 ms after stimulus presentation and earlier than 300 ms or 1000 ms, respectively) as well as wrong answers were counted as „misses". This data was analyzed for differences between groups using a t-test. As there were no significant differences between the groups of ASD subjects and TD controls, the behavioral data was not included as regressors of no interest in the ensuing analyses."

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[11] All following paragraphs that are highlighted with underscore and indicated with quotation marks have been cited verbatim from (Hoffmann et al., 2016). Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Journal of Neural Transmission, 123(8), 937-947. Reduced functional connectivity to the frontal cortex during processing of social cues in autism spectrum disorder. Hoffmann, E., Bruck, C., Kreifelts, B., Ethofer, T., & Wildgruber, D. Springer Vienna (2016). https://link.springer.com/journal/702

2.6.2.2. Laughter perception experiment

The behavioral data, i.e. the rating of valence of the laughter stimuli, was analyzed for possible differences between groups (TD vs. ASD) using a two-step ANOVA. Analyses were conducted with regard to the ratings of social inclusiveness with which laughter overall (Main ALL) was perceived. The data was also analyzed for differences between the individual laughter types and task instructions (JOY>TAU, JOY>TIC, TAU>TIC, SELF>OTHER). For a better overview, the statistical values of ratings for the individual laughter types and tasks are also displayed in Table 4.

In this analytical step, the behavioral data of all ten ASD subjects were analyzed, including the data of those excluded for the image analysis. Therefore, the behavioral data of ten ASD subjects and ten matched controls were analyzed.

The same analytical steps were conducted analogously for analyzing the reaction time.

2.6.3. Image analysis

2.6.3.1. Head motion analysis for both setups

„Head motion for all experimental conditions was analyzed for translational and rotational parameters and tested for differences between groups using a t-test[12]. Subjects showing a head movement exceeding 3 mm in any translational direction or more than 0.1° deviation in the rotation parameters were excluded from the ensuing analyses“ (an overview is given in Suppl. Tables 1 and 3).

In the first experimental setup, „one ASD subject exhibited excessive head movements under all three experimental conditions. Therefore, this data set had to be excluded from the study. A second ASD subject exceeded the inclusion parameters under one experimental condition, i.e. the experiment aimed at identifying face sensitive regions. This data set along with a data set of a corresponding TD control were excluded from this particular analysis, resulting

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in a reduced number of data sets for this experiment (n = 16 as opposed to n = 18 for the other tasks). In order to minimize the effect of movement artifacts on the ensuing analyses and to accommodate differences between groups, the individual movement parameters were included as regressors of no interest in the following steps of analysis“ of the first experimental setup.

In the experiment aimed at identifying regions that are involved in the perception and processing of different laughter types, two ASD subjects did exceed the accepted movement parameters, so their data sets were excluded from the analysis. Likewise, two controls did not meet the chosen criteria. This resulted in a number of 16 data sets which could be included in the analysis. As the excluded individuals were not identical in both experimental setups, a statistical analysis was conducted to confirm that both groups still matched in the second experimental setup (please refer to Table 2). As effects for this setup were expected to be smaller than in the audio-visual social perception experiment, no regressors of no interest were defined to include movement parameters in this analysis.

2.6.3.2. Image analysis - Audio-visual social perception experiment -

„Analyses of MRI images were conducted with the objective of examining differences in local brain activation as well as in functional connectivity. SPM8 was used to perform the analyses (Wellcome Department of Imaging Neuroscience, London, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/)[13]. Raw data first was preprocessed with the first 5 images of each run discarded to exclude measures preceding T1-equilibrium. Preprocessing steps included unwarping of images using a static field map, realignment, and coregistration with anatomical images, as well as normalization into the MNI space and smoothing with a Gaussian filter of 8 mm full width half maximum. Statistical inferences were based on a general linear model. Separate regressors were defined for each block within each experiment (i.e., faces, houses, objects,

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landscapes for the experiment aimed at identifying face processing regions (face-task); voices, animals, and environmental sounds for the task identifying voice processing areas (voice-task); A,V, and AV audiovisual integration experiments (AV-task);“ and SELF, OTHER, JOY, TAU, and TIC for the second experimental setup) „using a box car function convolved with the hemodynamic response function. Onsets were locked to the onset of each block, and modeled durations corresponded to the respective block’s duration. In order to balance serial autocorrelation within the data set, the error term was estimated as a first-order autoregressive process plus white noise (Friston et al., 2002). Time series were high-pass filtered to remove low frequency-noise (cut-off frequency: 1/128 Hz).“

- Region of interest definition

„In order to identify brain regions involved in the processing of faces, voices or audiovisual stimuli, the regressors described in the task section above were used to calculate the following target contrasts: FACES > HOUSES, OBJECTS, LANDSCAPES and VOICES > ENVIRONMENT, ANIMALS. For the audiovisual integration task, three contrasts were calculated: AV > A, AV > V, AV > A AND AV > V. Local brain activation in these contrasts were used for ROI definition. Activation patterns observed in the target contrasts were investigated at whole brain level. For the whole brain analysis, we defined as ROIs all brain regions significantly activated in all participants (ASD plus TD data sets) for the respective target contrast. Criteria for statistical significance in this case were set at a height threshold of $p < 0.001$, uncorrected, and a cluster extent corresponding to a $p < 0.05$ corrected for multiple comparisons across the whole brain (i.e., minimal cluster extent of $k \geq 67$ voxels for the face-task, $k \geq 63$ for the AV-task and $k \geq 66$ for the voice-task). Minimal cluster extent for each experimental task was analyzed using a script calculating the corrected cluster threshold (CorrClusTh, http://blogs.warwick.ac.uk/nichols/entry/spm5_gem_6/, (Nichols, 2010). Differences in the minimal cluster extent arise from small differences in smoothness of the data of each experimental task. Probably due to small sample size ($n = 18$ and $n = 16$ for the face task, respectively), activation of several regions known to be involved in the processing of human voices or faces (such as the amygdala or the fusiform gyrus) did not reach significance at this statistical threshold. Therefore, we additionally defined ROIs that exhibited activation under the respective target contrast and were located within these anatomical structures as identified by an anatomical labeling tool (Xjview SPM 8 toolbox). These ROIs were subjected to a small volume correction analysis that showed significant activation for all activation clusters within these target regions. For the small volume correction, anatomical regions as defined by the aal atlas (SPM8 toolbox) were used as masks.

Thus, there were 9 ROIs defined: left and right amygdala, left and right fusiform face area (face sensitive task), left and right mid superior temporal cortex (i.e. temporal voice area, TVA; voice sensitive task), and for the audiovisual integration task parts of the occipital lobe, bilateral temporal cortex areas and, using the conjunction, a small area in the right posterior superior temporal sulcus (rPSTS).“

- Differences in local brain activation

„In a following step, differences in local brain activation within these previously defined ROIs associated with autism were examined. Contrasts were subjected to two second-level analyses: one directly comparing activation patterns of the two groups in a two-sample t-test comparison and the other linking levels of brain activation with AQ scores via a correlation analysis.“

- Differences in functional connectivity - PPI-Analysis

„In order to analyze differences in functional connectivity depending on the stimulus type, psycho-physiological interaction analyses were conducted employing each of the above mentioned ROIs as a separate seed region.

For the PPI analysis, the time-course of the BOLD signal was employed as the physiological variable, more precisely, the time-course extracted from a 3 mm-sphere drawn around the individual peak-activation voxel within the ROIs. The different experimental conditions (e.g. faces, objects, landscapes etc.) were defined as separate psychological modulating variables and were contrasted analogously to the contrasts used in the categorical analysis of activation patterns ((1) FACES > HOUSES, ENVIRONMENT, LANDSCAPE; (2) VOICES > ENVIRONMENT, ANIMALS; (3) AV > A AND AV > V conjunction calculated using a minimal t statistic). As in this study a low-frequency stimulation experimental set-up, i.e. blocked design study, was used, the PPI could be calculated as the product of the deconvolved BOLD response time course and the vector of the psychological variables.

In a first level analysis approach, a single SPM model was calculated, using the psychological and the physiological variables and the psychophysiological interaction as separate regressors. Seed regions used in the PPI analysis were identical with the ROIs defined in the brain activation analysis at a statistical threshold of $p < 0.001$ and as presented in Table 6. All of the ROIs used as seeds in the PPI analysis had shown significant activation either at whole brain level or within the predefined regions using small volume correction (as explained above, see Table 6, Figure 10). Similar to the analysis of activation differences, in a second step two different approaches were used in analyzing ASD-related differences in functional connectivity: direct comparisons between the connectivity patterns of both groups (TD vs. ASD) as well as a correlation of connectivity measures and AQ scores measuring symptom severity (CorrAQ). In order to evaluate if the results of the correlation analysis were driven solely by group effects, individual beta values at local maxima of clusters exhibiting reduced connectivity with the PPI seed region were extracted for the respective PPI contrasts. Beta values were plotted against AQ scores and their correlation visualized graphically (Figure 12).

In order to increase the sensitivity of this analysis, PPI results were assessed at a height threshold of $p \leq 0.01$ uncorrected, with a cluster extent corresponding to $p \leq 0.05$ FWE corrected across the whole brain. All PPI results reported in this study were significant at whole brain level (Figure 11).

The reversed contrasts (TD < ASD and -CorrAQ) were used to investigate whether ASD subjects showed any increase in connectivity as compared to TD controls (TD < ASD) or whether a high AQ score was correlated with a reduced connectivity (CorrAQ).“

2.6.3.3. Image analysis - Laughter perception experiment -

The image analysis of the second experimental setup was conducted analogously to the analysis described in detail under 2.6.3.2., albeit with different regressors. Due to movements exceeding the set limits, only sixteen data sets could be included in the analyses (8 ASD and 8 TD controls, for the matching data please refer to Table 2. An overview of movement data is given in Suppl. Table 3). For the ensuing fMRI data analysis, the statistical threshold was set at $p < 0.001$, uncorrected, with a cluster extend corresponding to a $p < 0.05$ corrected for multiple comparisons across the whole brain. Minimal cluster extent was calculated using the script by Nichols (Nichols, 2010) and is individually indicated for each target contrast (compare Fig. 13, 14, 15, 16). For the analysis, five different regressors were defined. Three regressors were aimed at identifying areas involved in the perception and processing of laughter: TIC (tickling laughter), JOY (socially including, e.g. joyful, friendly laughter), TAU (socially excluding, e.g. taunting laughter). Two regressors were aimed at the investigation of possible differences in brain activation under two different mentalizing task conditions: SELF (laughter imagined as being directed at the observer), and OTHER (observer witnessing an actor practicing different types of laughter). No regressors of no interest were defined.

Table 2. Participants' age and scores yielded in intelligence tests - matching data for the second experimental setup

	ASD subjects	**SD**	**TD controls**	**SD**	**t-value**	**p-value**	**Cohen's d**
Age (years)	32.13	10.6	31.63	11.8	-0.09	0.93	-0.05
WAIS[1] - (verbal) Percentile	51.63	33.3	62.58	31.1	0.68	0.51	0.34
WAIS - (operational) Percentile	52.38	38.6	55.25	26.0	0.18	0.86	0.09

1 WAIS - Wechsler Adult Intelligence Scale, all participants had at least successfully completed secondary school. Degrees of freedom t (16).

- Differences in local brain activation

The first analytical step of the image analysis was aimed at identifying ASD-related differences in activation patterns in response to laughter in general (Main ALL). In a second step, task-related differences in activation were investigated as well as, in an explorative approach, differences between the individual laughter types. Therefore, the following contrasts were calculated and analyzed for group differences (TD vs. ASD) by comparing activation patterns of the two groups using a two-sample t-test:

1) Analysis of activation patterns elicited in response to all laughter types (Main ALL).
2) Analysis of task-specific activation patterns (SELF vs. OTHER).
3) Analysis of differences between the activation patterns in response to specific laughter types - namely, JOY vs TAU, JOY vs. TIC, TAU vs. TIC.

Also, the reversed contrasts (ASD vs. TD) were analyzed in order to investigate whether ASD subjects showed higher activation than TD controls in any of these contrasts. For all clusters, the statistical threshold was set at $p < 0.001$ at whole-brain level. The minimal cluster extent is indicated in the respective Figure (Figure 13).

- Differences in functional connectivity - PPI-Analysis

In a second step of the image analysis, the connectivity between brain regions involved in the processing of laughter was analyzed using psycho-physiological interaction analysis, analogously to the PPI-analysis conducted for the first experiment. Differences in functional connectivity were analyzed for the perception of laughter over all and for mentalizing tasks and laughter types contrasted with each other.

In a first step of the PPI-analysis, the three different laughter types (TIC, JOY, TAU) and the two conditions of the mentalizing tasks (SELF, OTHER) were defined as independent psychological modulating variables. The contrasts for which connectivity analysis was conducted were chosen in accordance with those calculated in the activation analysis. Again, the PPI was calculated as the product of the deconvolved BOLD response time course and the vector of the psychological variables.

The different psychological, physiological variables and the psychophysiological interaction - all separate regressors - were used to calculate a single level SPM model. The seed regions used in this second PPI analysis were identical with the ROIs used in the first PPI analysis (compare Table 6). Thus, seven seed regions were defined: left and right amygdala, left and right FFA, left and right TVA, and the right pSTS. For each seed region and contrast, a separate analysis was conducted. All connectivity patterns were analyzed for group differences (TD vs. ASD and the reversed contrast ASD vs. TD). In detail, the following analyses were conducted:

1) Analysis of connectivity of the seven seed regions with other brain regions when being presented with all types of laughter (Main ALL).
2) Analysis of connectivity modulated by different mentalizing tasks (SELF vs. OTHER).
3) Comparison of connectivity in response to different types of laughter, as compared to each other (JOY vs. TAU, JOY vs. TIC, TAU vs. TIC,).

The statistical threshold was set at $p \leq 0.001$ uncorrected, with a cluster extent corresponding to $p \leq 0.05$ FWE corrected across the whole brain. Only results that were significant at whole brain level were reported (Figure 14, 15, 16).

3. Results

3.1. Statistical analysis of questionnaire results

Table 3. Statistical evaluation of the conducted questionnaires.

	ASD subjects	SD	TD controls	SD	t-value	p-value	Cohen‘s d
gelotophobia[3]	2.83	0.50	1.56	0.41	-5.84	0.00*	-2.77
gelotophilia	1.67	0.23	2.26	0.61	2.73	0.02*	1.28
katagelasticism	1.84	0.66	2.07	0.66	0.74	0.47	0.35
ICQ-I[2]	-0.52	1.57	0.92	1.06	2.27	0.04*	1.08
ICQ-N	-0.03	1.89	0.88	1.16	1.22	0.24	0.58
ICQ-D	0.04	1.79	1.10	1.26	1.45	0.17	0.68
ICQ-E	0.17	1.42	1.63	1.51	2.11	0.05*	1.00
ICQ-C	0.32	1.61	0.97	1.32	0.94	0.36	0.44
BDI[1]	11.56	8.99	2.67	1.80	2.91	0.02*	-1.37
LSAS-A[4]	32.44	13.65	8.44	9.40	4.35	0.00*	-2.05
LSAS-V	36.22	13.28	11.78	12.51	4.03	0.00*	-1.89
LSAS-TOT	68.67	25.00	20.22	21.36	4.42	0.00*	-2.08
MSCEIT-B1[5]	106.13	11.89	109.50	13.45	-0.53	0.60	0.27
MSCEIT-B2	104.13	18.26	107.13	9.23	-0.41	0.69	0.21
MSCEIT-B3	97.50	15.51	105.38	16.21	-0.99	0.34	0.50
MSCEIT-B4	88.25	22.70	103.38	12.05	-1.67	0.13	0.83
MSCEIT-EXP	106.25	9.47	110.25	10.98	-0.78	0.45	0.39
MSCEIT-REA	90.25	17.10	105.63	13.06	-2.02	0.06	1.01
MSCEIT-TOT	99.75	12.42	110.00	10.62	-1.77	0.10	0.89

*Overview of the statistical evaluation of the conducted questionnaires and group comparison: 1 - BDI, Beck Depression Inventory; 2 - ICQ, Interpersonal Competence Questionnaire, testing five dimensions, I - Initiation, N - Negative Assertion, D - Disclosure, E - Emotional Support, C - Conflict Management; 3 - gelotophobia, gelotophilia and katagelasticism were tested for by the PhoPhiKat; 4 - LSAS, Liebowitz Social Anxiety Scale, LSAS-A, testing for anxiety experienced in social situations or when performing actions, LSAS-V, testing for avoidance of social situations or actions, LSAS-TOT, combination of the anxiety and avoidance scores; 5 - Mayer-Salovey-Caruso Emotional Intelligence Test, B1 - 1st branch, correct perception of emotions, B2 - 2nd branch, use of emotions and their integration into thoughts, B3 - 3rd branch, understanding causes underlying emotions, B4 - 4th branch, management of emotions, TOT - total score calculated using all four branches. * statistically significant difference between the ASD subjects and the TD control group, corresponding to a significance level of* $p < 0.05$.

3.1.1. Analysis of gelotophobia, gelotophilia and katagelasticism

A significant difference in gelotophobia between groups could be found (p<0.002, compare Table 3). Higher values for gelotophobia could be observed in the ASD group (∅2.83 as compared to ∅1.56 in the TD group). In total, two ASD subjects reached values that are concordant with no gelotophobia (< 2.5). Four subjects exhibited slight gelotophobia (2.5 - 3.0) and three subjects yielded scores that are consistent with marked gelotophobia (3.0 - 3.5). In the TD group, there was not a single subject whose scores reached the cut-off value for gelotophobia of 2.5.

Also, a significant difference in gelotophilia scores was found (∅1.67 in the ASD and ∅2.26 in the TD group), reflecting a reduced joy of being laughed at in the ASD group as compared to TD controls. Regarding katagelasticism, no difference between groups was found. The results of the group comparison are also illustrated in Fig 6.

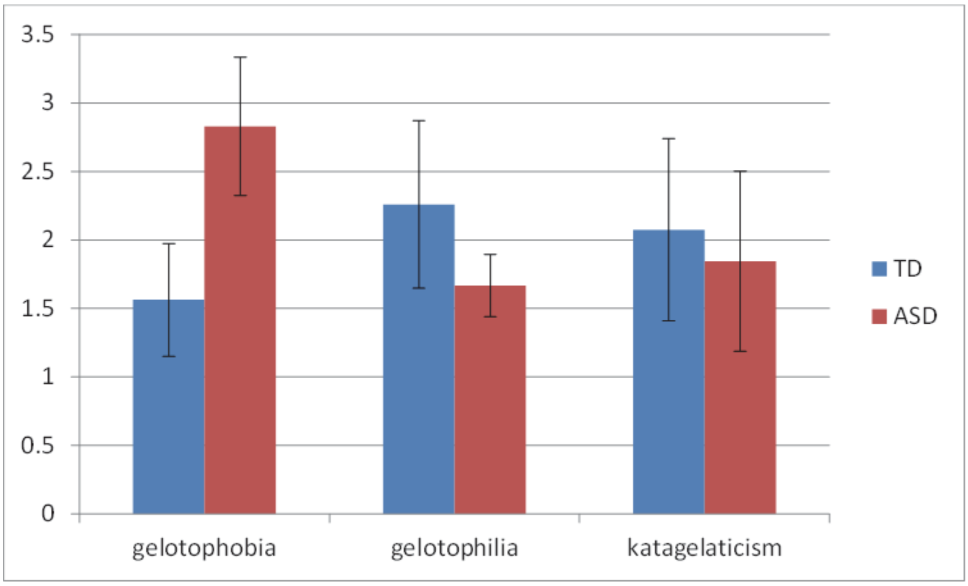

Figure 6. Group comparisons between ASD subjects and TD controls regarding gelotophobia, gelotophilia, and katagelasticism. The scores aimed at measuring gelotophobia showed a significant difference between groups (p < 0.002). For gelotophilia, a significant difference between groups was found as well (p < 0.02). For detailed information regarding scores and p-values, please refer to Table 3. TD controls represented in blue, ASD subjects represented in red.

3.1.2. Analysis of the Interpersonal Competence Questionnaire (ICQ)

In two of the five different domains of interpersonal competence, a statistically significant difference between groups could be found (initiation and emotional support). Here, ASD subjects yielded significantly lower scores than TD controls (ICQ-I: ASD ∅-0.52, TD ∅0.92; ICQ-E: ASD ∅0.17, TD ∅1.63). In all domains, values in the TD group were higher as compared to the ASD group (please compare Figure 7 and Table 3). However, in the other three branches, this difference did not meet the statistical threshold of $p < 0.05$.

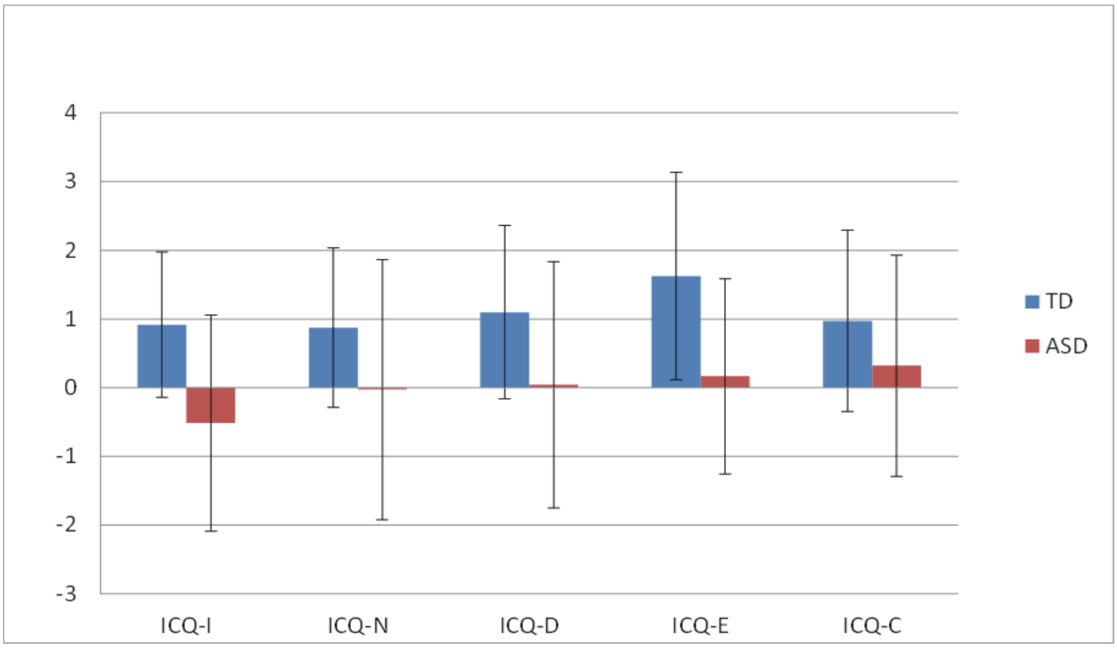

Figure 7. ICQ, Interpersonal Competence Questionnaire, I - Initiation, N - Negative Assertion, D - Disclosure, E - Emotional Support, C - Conflict Management. No significant difference between groups could be found in any of the categories. Score values and detailed statistical information is given in Table 3. TD controls represented in blue, ASD subjects represented in red.

3.1.3. Analysis of the Beck Depression Inventory

In this test, ASD subjects reported significantly more depressive symptoms than the participants in the control group (ASD ∅11.56 as compared to ∅2.67 in controls, Table 3 and Figure 8). In the TD control group, no one yielded a score higher than 5, corresponding to minimal depressive symptoms. Two TD subjects reported no depressive symptoms whatsoever and five scored 3 points or less.

In the ASD group, four participants yielded a score concordant with a minimal depression (< 9 points). Another four subjects showed symptoms of a mild depression (scores 10 - 18 points) and one exhibited severe depressive symptoms (> 30 points).

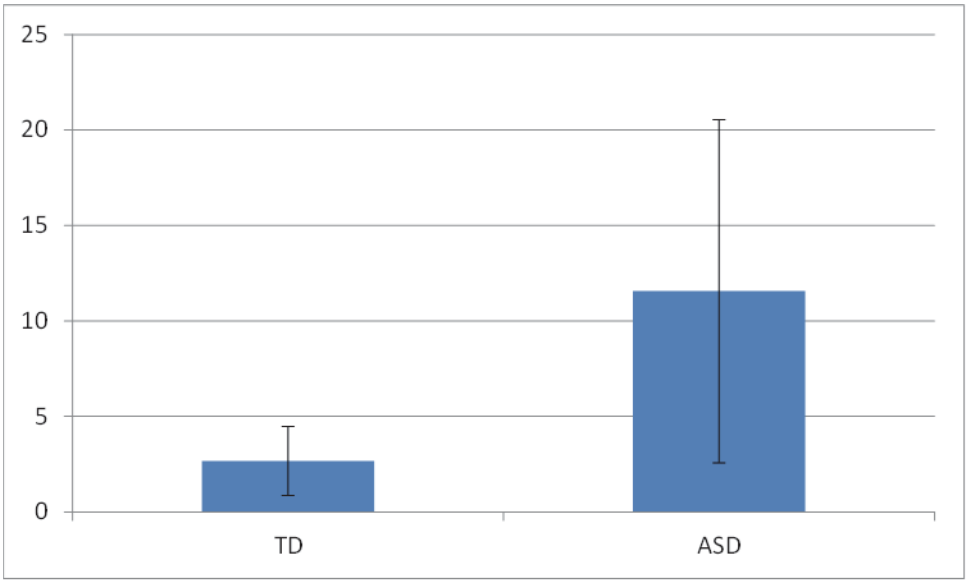

Figure 8. As expected, ASD subjects reported more depressive symptoms than their TD controls (ASD scored ∅11.56 as compared to ∅2.67 points in controls; $p < 0.02$)

3.1.4. Analysis of the Liebowitz Social Anxiety Scale

Three different scores were calculated, measuring the anxiety in social situations and in performing certain tasks, the avoidance of these circumstances, and a total score combining both. In all three dimensions ASD subjects scored significantly higher than their TD controls (for all branches $p<0.01$; compare Table 3 and Figure 9).

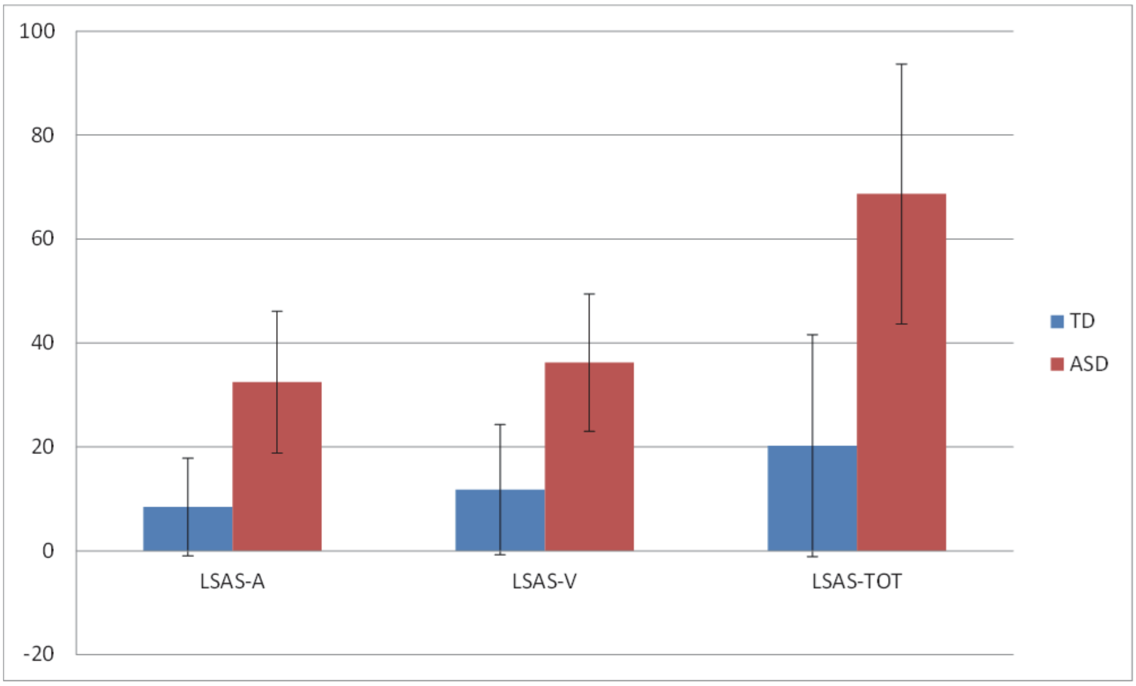

Figure 9. LSAS, Liebowitz Social Anxiety Scale, LSAS-A, testing for anxiety perceived in social situations or when performing actions, LSAS-V, testing for avoidance of social situations or actions, LSAS-TOT, combination of the anxiety and avoidance scores. ASD subjects scored significantly higher in all three sub-tests ($p<0.01$ in all sub-tests; please compare Table 3) TD controls represented in blue, ASD subjects represented in red.

3.1.5. Analysis of the Mayer-Salovey-Caruso Emotional Intelligence Test

Four different branches of emotional intelligence were tested for in this questionnaire - perception of emotions, the use of emotions and their integration into one's thoughts, understanding the underlying causes of emotions, and the management of emotions. The first two branches are combined in an „experiential" score (EXP). The latter two branches are reflected in the „strategic" score (REA). A total score (TOT) was also calculated integrating the outcome of all four branches.

In the first four branches, only very modest differences between groups could be found. Here, TD controls scored minimally higher, although this slight difference was far from significance. In the „strategic" score, testing for the understanding and management of emotions, there was a more pronounced distinction between the two groups, with the p-value showing a trend towards significance ($p<0.06$, compare Table 3).

3.2. Analysis of behavioral data

- *Audio-visual social perception experiment*

„The analyses of both conditions for which behavioral data were recorded showed no significant differences between the groups of ASD subjects and TD controls (Suppl. Table 2)[14]. However, under the experimental condition aimed at identifying face sensitive regions, ASD subjects were slightly better in correctly discerning stimuli that were repeated immediately, although this difference was only at trend level and did not reach statistical significance not significant“ ($p < 0.08$, Cohen‘s d -0.203).

\- *Laughter perception experiment*

The behavioral data, i.e. the rating of laughter types, was analyzed for differences between groups. Analyses were conducted with regard to the ratings on the social inclusiveness of the different laughter types. In a second step, reaction times were analyzed accordingly (an overview of both rating and reaction time is presented in Tables 4 and 5). As unidirectional hypotheses were tested, the presented p-values express the significance level for the tested directional hypothesis.

There was no significant difference between groups in the overall rating of laughter (main_ALL). There was one significant difference between both groups in the rating of the individual laughter types, with ASD subjects rating significantly higher scores for socially including laughter (∅ 2.18, SD±0.36 as compared to TD controls ∅1.85, SD±0.35). Both groups rated higher scores for socially excluding laughter as compared to socially including and tickling laughter. There was a slight difference between groups, however, here, the differences between groups did not reach a significant level. Tickling laughter, in turn, was rated higher than socially including laughter, but not as high as socially excluding laughter.

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[14] All following paragraphs that are highlighted with underscore and indicated with quotation marks have been cited verbatim from (Hoffmann et al., 2016). Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Journal of Neural Transmission, 123(8), 937-947. Reduced functional connectivity to the frontal cortex during processing of social cues in autism spectrum disorder. Hoffmann, E., Bruck, C., Kreifelts, B., Ethofer, T., & Wildgruber, D. Springer Vienna (2016). https://link.springer.com/journal/702

In the analysis of contrasts of different laughter types, only one significant difference between groups could be observed. In the rating of inclusive laughter as compared to excluding laughter, the difference between the rating of the two laughter types was smaller in the ASD group (∅-0.90, SD±0.24) than in the TD control group (∅-1.26, SD±0.49).

In the reaction time analysis, no difference between groups was found for the reaction time in response to laughter over all (main_ALL). Although ASD subjects generally showed longer reaction times than controls, this difference was small and did not reach statistical significance. In the analysis contrasting the reaction time with regard to different laughter types, there was no significant difference between groups, either.

3.3. Analysis of fMRI data

3.3.1. Analysis of head movement

- Audio-visual social perception experiment

„The detailed statistical results of the head movement analysis for all experimental conditions are shown in Suppl. Table 1[15]. In general, ASD subjects showed slightly larger movements than TD controls, although this difference was not significant for most parameters. A significant difference in head movements between groups could be observed for the translation in the direction of the x-axis ($p < 0.039$) as well as for the z-rotation (i.e. yaw, $p < 0.049$) in the experiment aimed at identifying face sensitive regions. A significant difference in z-rotation between groups was also found under the experimental condition identifying voice sensitive regions ($p < 0.047$). There were no differences between groups under the experimental condition aimed at identifying regions involved in the processing of audiovisual signals, although differences in x-translation exhibited a p-value approaching significance ($p < 0.068$).“

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[15] All following paragraphs that are highlighted with underscore and indicated with quotation marks have been cited verbatim from (Hoffmann et al., 2016). Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Journal of Neural Transmission, 123(8), 937-947. Reduced functional connectivity to the frontal cortex during processing of social cues in autism spectrum disorder. Hoffmann, E., Bruck, C., Kreifelts, B., Ethofer, T., & Wildgruber, D. Springer Vienna (2016). https://link.springer.com/journal/702

Table 4. Statistical evaluation of ratings with regard to laughter type and task

Rating	ASD	SD	TD	SD	t value	p value	Cohen‘s d
main ALL	2.62	0.40	2.47	0.22	1.05	0.16	-0.53
main JOY	2.18	0.36	1.85	0.35	2.07	**0.03***	-0.93
main TAU	3.08	0.33	3.11	0.34	-0.20	0.43	0.12
main TIC	2.60	0.60	2.45	0.35	0.69	0.25	-0.23
main SELF	2.65	0.42	2.47	0.34	1.080	0.15	-0.47
main OTHER	2.58	0.39	2.47	0.20	0.83	0.21	-0.35
JOY vs TAU	-0.90	0.24	-1.26	0.49	2.09	**0.03***	-0.93
JOY vs TIC	-0.43	0.42	-0.60	0.51	0.81	0.22	-0.36
TAU vs TIC	0.48	0.39	0.66	0.37	-1.06	0.15	0.47
SELF vs OTHER	0.07	0.18	0.00	0.34	0.59	0.28	-0.25

*JOY - socially including laughter, TAU - socially excluding laughter, TIC - tickling laughter; n(ASD) =10. * Statistically significant results.*

Table 5. Evaluation of reaction time with regard to laughter type and task

Reaction time	ASD	SD	TD	SD	t value	p value	Cohen‘s d
main ALL	2854	659	2714	840	0.42	0.34	-0.19
main JOY	2858	582	2672	839	0.58	0.29	-0.26
main TAU	2744	677	2619	790	0.38	0.36	-0.17
main TIC	2961	737	2850	926	0.30	0.39	-0.13
main SELF	2861	649	2648	865	0.62	0.27	-0.28
main OTHER	2849	695	2780	884	0.19	0.43	-0.09
JOY vs TAU	99	195	53.6	285	0.40	0.35	-0.19
JOY vs TIC	-95	258	-178	232	0.74	0.24	-0.34
TAU vs TIC	-194	126	-231	254	0.41	0.35	-0.19
SELF vs OTHER	-10	268	-132	481	0.67	0.26	-0.31

Reaction times measured in milliseconds. JOY - socially including laughter, TAU - socially excluding laughter, TIC - tickling laughter; n(ASD) = 10.

- Laughter perception experiment

For a detailed description of the head movement data observed in the experiment using laughter as stimuli, please refer to Suppl. Table 3. As in the first experimental setup, ASD subjects generally exhibited larger movements than TD controls. In the first block of stimulus presentation, a significant difference between groups could be observed in the x-translation and the y-rotation (p-values $p < 0.05$ and $p < 0.03$, respectively). In the z-rotation, the p-value was approaching the statistical threshold ($p < 0.07$). In the second session, significant differences between groups could be observed in the x-translation ($p < 0.01$) and in the z-rotation ($p < 0.015$). In the y-rotation, the difference was bordering on the statistical threshold ($p < 0.059$).

3.3.2. Image analysis - Audio-visual social perception experiment

3.3.2.1. Regions of interest definition

„The perception of faces as compared to houses, landscapes or objects (FACES > HOUSES, OBJECTS, LANDSCAPE) yielded increases in activation namely in the left and right amygdala and the left and right fusiform gyrus[16].

The processing of voices as compared to environmental or animal sounds (VOICES > ENVIRONMENT, ANIMALS) yielded increasing activation in the left and right mid superior temporal cortex (temporal voice area, TVA).

By using the AV > A AND AV > V conjunction, part of the right posterior superior temporal cortex (pSTC) was identified as a region contributing to audiovisual integration processes. The contrast AV > A yielded activation in the occipital brain region; the contrast AV > V showed activation in the left and right temporal cortex.

For a more comprehensive overview of the results yielded in the activation analyses, please refer to“ Table 6 and Figure“ (10a) - 10c)).

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[16] All following paragraphs that are highlighted with underscore and indicated with quotation marks have been cited verbatim from (Hoffmann et al., 2016). Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Journal of Neural Transmission, 123(8), 937-947. Reduced functional connectivity to the frontal cortex during processing of social cues in autism spectrum disorder. Hoffmann, E., Bruck, C., Kreifelts, B., Ethofer, T., & Wildgruber, D. Springer Vienna (2016). https://link.springer.com/journal/702

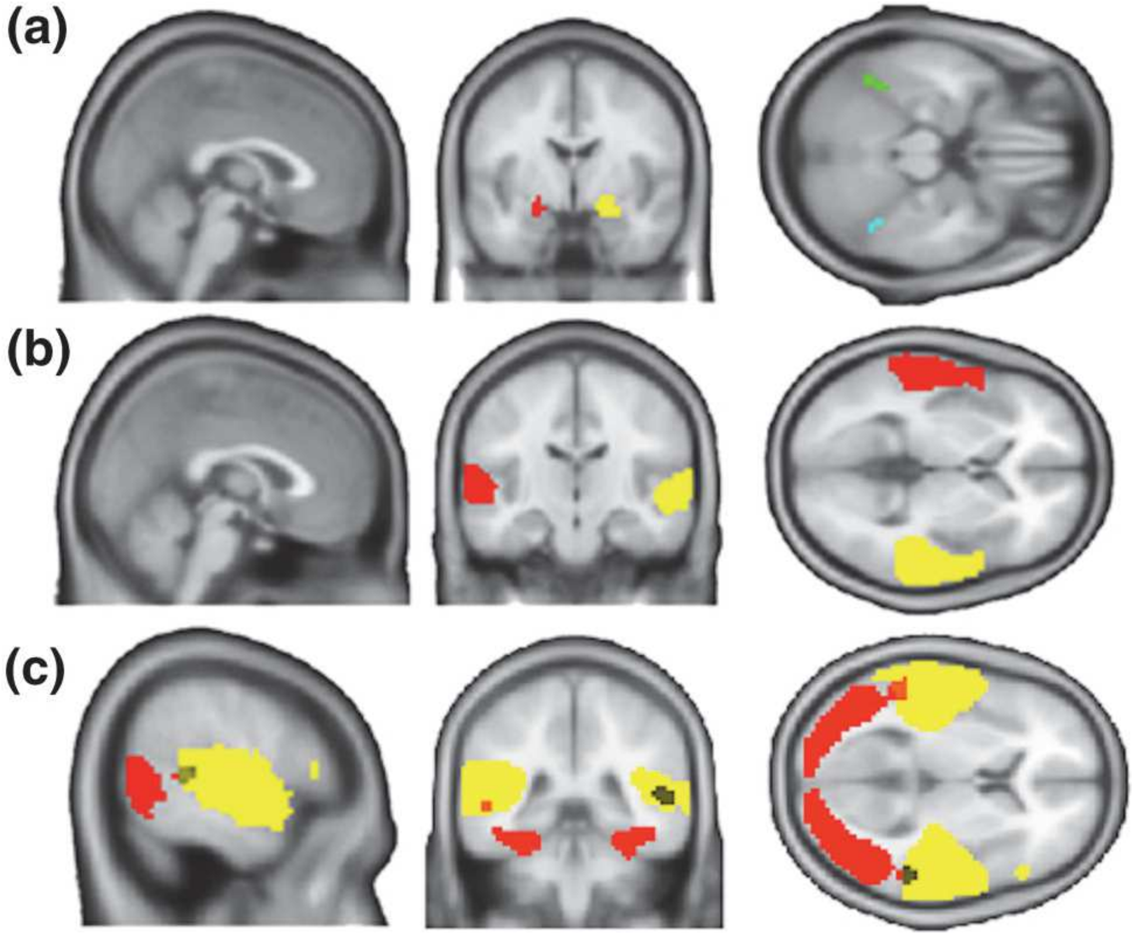

Figure 10. Activation analysis and region of interest definition – face sensitive and voice sensitive regions.

10„a) Face sensitive regions: Brain areas showing increased activation to pictures of faces as compared to pictures of landscapes, houses, or objects: left amygdala (depicted in red), right amygdala (yellow), left FFA (green), right FFA (blue). **b)** Voice sensitive regions: Brain areas showing increased activation to human voices as compared to environmental or animal sounds: left TVA (red), right TVA (yellow). **c)** Audiovisual integration areas: Brain areas showing increased activation to audiovisual as compared to auditory or visual stimulation: AVminusA (red), AVminusV (yellow), AV > V ∩ AV > A conjunction (grey). For all contrasts, $p < 0.001$.“

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Table 6. Differential hemodynamic activation following the perception of different functional experiments aimed at identifying face-, voice- and audiovisual-sensitive areas.

Contrasts	**x**	**y**	**z**	**Z-score (peak voxel)**	**Cluster size (voxel)**
FACE (faces > houses, object, landscapes)					
left amygdala (*)[4], limbic lobe, parahippocampal gyrus, hippocampus	-21	-6	-12	3.87	61
right amygdala*, limbic lobe, parahippocampal gyrus, hippocampus	24	-9	-12	4.66	83
left FFA[1,4] (left fusiform gyrus, cerebellum posterior lobe)	-39	-48	-24	3.43	21
right FFA[4] **(**right fusiform gyrus, brodmann area 37)	42	-48	-24	4.24	19
VOICE (voices > animals, environmental sounds)					
left TVA[2]***** (left superior temporal gyrus, middle temporal gyrus, brodmann areas 22 and 21)	-60	0	-9	5.52	819
right TVA* (right superior temporal gyrus, middle temporal gyrus, brodmann areas 21 and 22)	60	3	-9	5.73	867
Audio-visual integration					
AVminusA*	48	-69	-6	7.24	5430
AVminusV*	51	-12	-3	7.56	2075
AV minus V ∩ AV minus A[3,4]	54	-39	9	3.72	30

„*1 - FFA - fusiform face area. 2 - TVA - temporal voice area. 3 - this conjunction was calculated using a minimum t statistic. *ROI significant at whole brain level. (*) ROI significant at trend level (p < 0.066). 4 - significant for small volume correction. Activation thresholded at p < 0.001, uncorrected, with a minimal cluster extent of k ≥ 67 voxels for the face-task, k ≥ 63 for the AV-task and k ≥ 66 for the voice-task at whole brain level, corresponding to p < 0.05 FWE corrected for multiple comparison across the whole brain. Coordinates according to the MNI system.*" Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Journal of Neural Transmission, 123(8), 937-947. Reduced functional connectivity to the frontal cortex during processing of social cues in autism spectrum disorder. Hoffmann, E., Bruck, C., Kreifelts, B., Ethofer, T., & Wildgruber, D. Springer Vienna (2016). https://link.springer.com/journal/702

3.3.2.2. ASD-related differences in local brain activation

„The group comparison TD > ASD showed no significant activation differences between ASD and TD individuals. Moreover, the correlation analyses (CorrAQ) failed to show significant association between local brain activation and AQ scores.“[17]

3.3.2.3. ASD-related differences in functional connectivity

„PPI FACES: For the group comparison TD > ASD the following seed regions were used: left and right amygdala and the left and right fusiform gyrus. These analyses yielded no significant results, neither in the group contrast nor in the correlation analysis.

PPI VOICES: The PPI analyses using the left and right TVA - identified using the contrast condition human sounds vs. other sounds (VOICES > HOUSES, OBJECTS, LANDSCAPE) - as seed regions showed reductions in connectivity in ASD subjects. In the analysis using the left TVA as seed region, a reduction in connectivity between the left TVA and the frontal cortex, namely the superior and medial frontal gyrus, was observed in the ASD as compared to the TD group when listening to voices as compared to other sounds. Furthermore, a negative correlation between AQ scores and the connectivity between the left TVA and medial frontal gyrus and the limbic lobe as well between the right TVA and the frontal lobe, anterior part of caudate and limbic lobe was observed when listening to voices rather than to other sounds (-CorrAQ; Figure 11a) - 11c), Table 7).

PPI AV INTEGRATION: This analysis using the occipital lobe, left and right temporal cortex and the right audiovisual integration area as a seed region yielded no results meeting the chosen statistical criteria.“

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[17] All following paragraphs that are highlighted with underscore and indicated with quotation marks have been cited verbatim from (Hoffmann et al., 2016). Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Journal of Neural Transmission, 123(8), 937-947. Reduced functional connectivity to the frontal cortex during processing of social cues in autism spectrum disorder. Hoffmann, E., Bruck, C., Kreifelts, B., Ethofer, T., & Wildgruber, D. Springer Vienna (2016). https://link.springer.com/journal/702

3.2.2.4. Evaluation of individual beta values of PPI correlation analysis

„For the PPI correlation analysis contrasts using the left TVA and the right TVA as seed regions, beta values were plotted against AQ scores [%]. For both contrasts, a negative correlation between AQ scores and beta values was found, i.e. the higher the score in the AQ, the more reduced the connectivity to the frontal cortex“ (see Figure 12a) and 12b)).

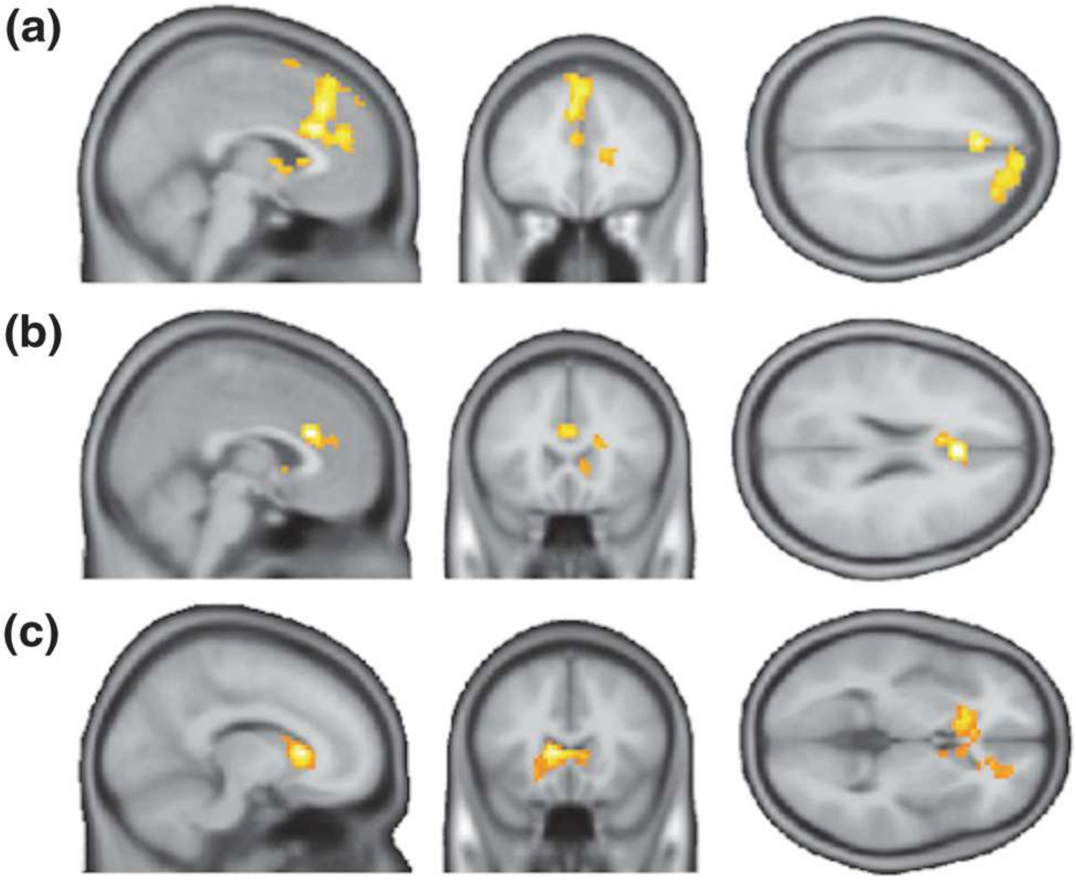

Figure 11a) Connectivity of the left TVA (Group contrast TD vs ASD): A reduction in connectivity between the left TVA and the frontal cortex (superior and medial frontal gyrus) in ASD subjects as compared to TD controls could be observed. Local maximum: x: 0, y: 24, z: 24.
11b) Connectivity of the left TVA (Correlation with AQ): A negative correlation between individual beta values and AQ scores were observed in this contrast, between the left TVA and the limbic lobe, anterior cingulate, and the medial frontal gyrus. Local maximum: x: 3, y: 27, z: 24.
11c) Connectivity of the right TVA (Correlation with AQ): A reduction in connectivity between the right TVA and frontal brain regions (frontal lobe, caudate, limbic lobe, medial frontal gyrus) correlated with individual AQ scores was found. Local maximum: x: -12, y: 21, z: 6.
For all contrasts, $p < 0.01$.“ https://link.springer.com/journal/702

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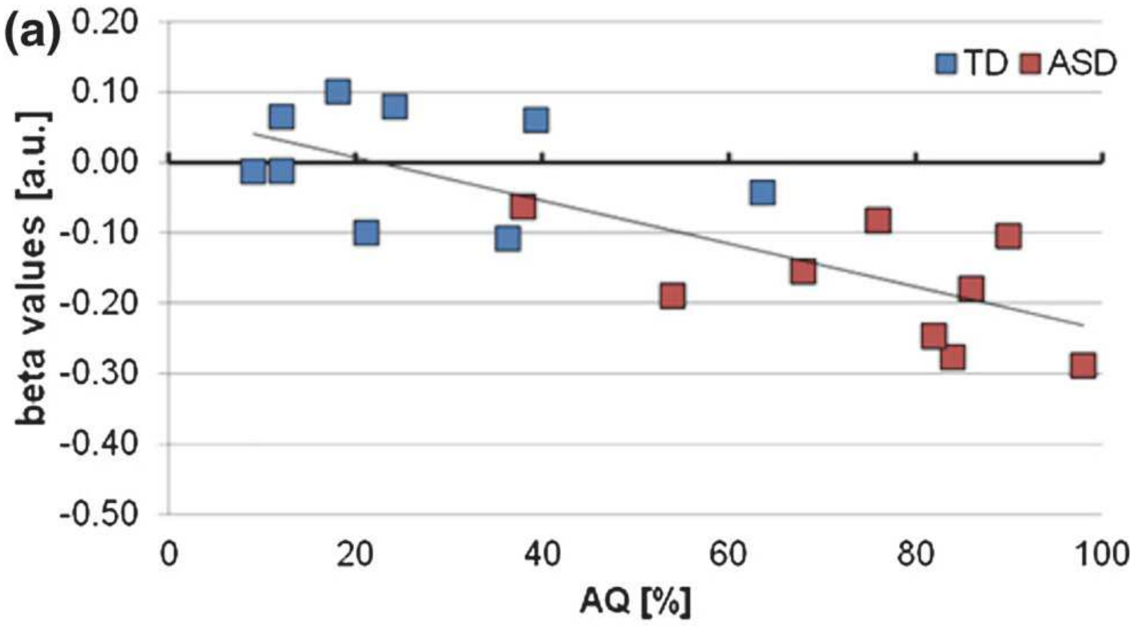

Figure 12 „**(a)** Connectivity of the left TVA. Beta values were extracted at individual local maximum using the contrast image shown in 2b) as mask and plotted against corresponding AQ scores [%]. ASD subjects represented by red dots, TD controls represented by blue dots."

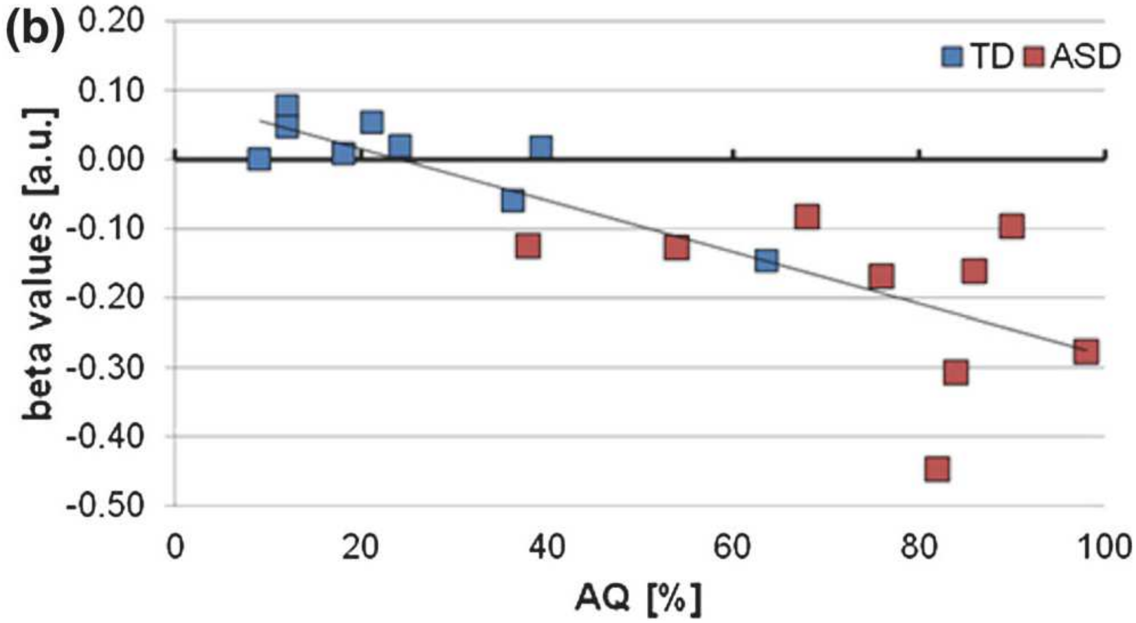

Figure 12 „**(b)** Connectivity of the right TVA. Beta values were extracted at individual local maximum using the contrast image shown in 2c) as mask and plotted against corresponding AQ scores [%]. ASD subjects represented by red dots, TD controls represented by blue dots."

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Table 7. PPI analyses results. Regions exhibiting decreased relative connectivity with previously defined seed regions

Contrasts	x	Y	z	Z-score (peak voxel)	Cluster size (voxel)
Group comparison (TD > ASD)					
left TVA[1] ➡ superior frontal gyrus, medial frontal gyrus, limbic lobe, anterior cingulate, caudate	0	24	24	4.04	1112
Correlation Analysis with AQ					
left TVA ➡ limbic lobe, anterior cingulate, medial frontal gyrus, brodmann area 24 and 32	3	27	24	4.25	326
right TVA ➡ frontal lobe, caudate, limbic lobe, anterior cingulate, caudate head, medial frontal gyrus, superior frontal gyrus	-12	21	6	4.37	400

„1- TVA - temporal voice area. Statistical threshold was set at p < 0.01, uncorrected, FWE of p < 0.05, corrected for multiple comparisons across the whole brain at the cluster level. Coordinates according to the MNI system.“ https://link.springer.com/journal/702

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3.3.3. Image analysis - Laughter perception experiment

3.3.3.1. ASD-related differences in local brain activation

In the contrast combining activation patterns in response to all three types of laughter (Main ALL), TD controls showed a higher activation than ASD subjects in the left inferior frontal gyrus within brodmann area 47 (compare Table 8 and Figure 13).

However, no significant differences in brain activation patterns were found between both groups related to task specific differences or stimulus specific differences (i.e. main effects (JOY, TAU, TIC, SELF, OTHER) and contrasts: SELF vs. OTHER, JOY vs. TAU, JOY vs. TIC, TAU vs. TIC).

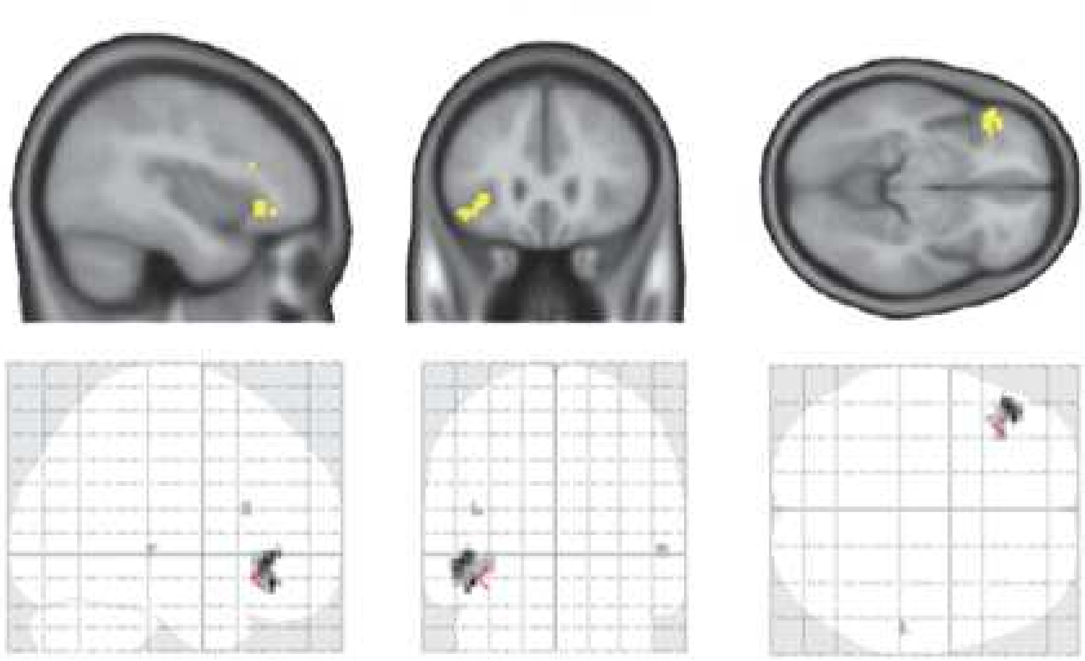

Figure 13. Group comparison TD vs. ASD under the contrast condition Main ALL. Comparison of activation patterns during the perception of all three laughter types showed a higher activation in the left inferior frontal gyrus (Brodmann area 47) in the group of TD controls as compared to ASD subjects. Local maximum x: -42, y: 36, z: -12, minimal cluster extent 71 voxel.

Table 8. Group contrast TD > ASD - Differential hemodynamic activation in response to all types of laughter (contrast Main ALL).

	x	Y	z	Z-score	Cluster size (voxel)
Group comparison TD > ASD					
Contrast Main ALL Left inferior frontal gyrus, brodmann area 47	-42	36	-12	4.01	79

3.3.3.2. ASD-related differences in functional connectivity

The connectivity analysis using PPI analysis and seven different seed regions yielded several significant differences between groups (compare Table 9).

- Group comparison TD > ASD:

In the contrast combining all three laughter types (Main ALL), a higher connectivity between the left TVA and the middle frontal gyrus could be observed in the TD group as compared to ASD subjects. Also, an increased connectivity was found between the left TVA and the middle occipital gyrus, as well as between the left TVA and the left parietal lobe and precuneus, and between the left TVA and the left limbic lobe and cingulate gyrus (results are displayed in Figure 14).

When contrasting socially excluding laughter with including laughter (TAU>JOY), a higher connectivity between the right amygdala and the right frontal lobe, the right precentral gyrus, and the right superior temporal gyrus could be observed in the TD controls as compared to ASD subjects (Figure 15). In the reverse contrast, contrasting socially including laughter with excluding laughter (JOY > TAU), a higher connectivity between the right FFA and the right inferior frontal gyrus and precentral gyrus was found in the TD group as compared to the ASD group. Connectivity was furthermore increased between the right FFA and the left inferior frontal gyrus as well as between the right FFA and the left parietal lobe and the precuneus (compare Figure 16).

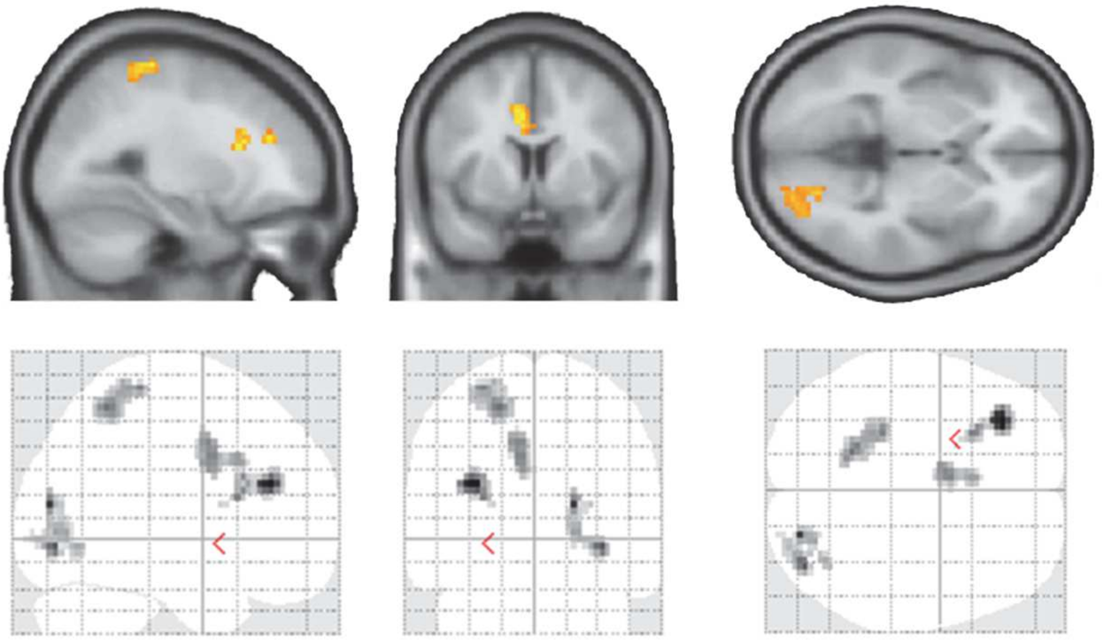

Figure 14. Group differences in connectivity patterns during perception of all laughter types (TD (Main ALL) > ASD (Main ALL)), PPI using the left TVA as a seed region. Here, an increase in connectivity between the left TVA and four other areas of the brain was found. Connectivity was increased towards: the middle frontal gyrus (local maximum x: -33, y: 36, z: 24), the middle occipital gyrus (x: 21, y: -81, z: 15), the left parietal lobe and precuneus (x: -18, y: -51, z: 57), as well as towards the left limbic lobe and cingulate gyrus (x: -6, y: 6, z: 12). Above, areas with an increase in connectivity are superimposed on a mean anatomical image, below, an overview is given using a transparent depiction of the brain. Minimal cluster extent 74 voxel.

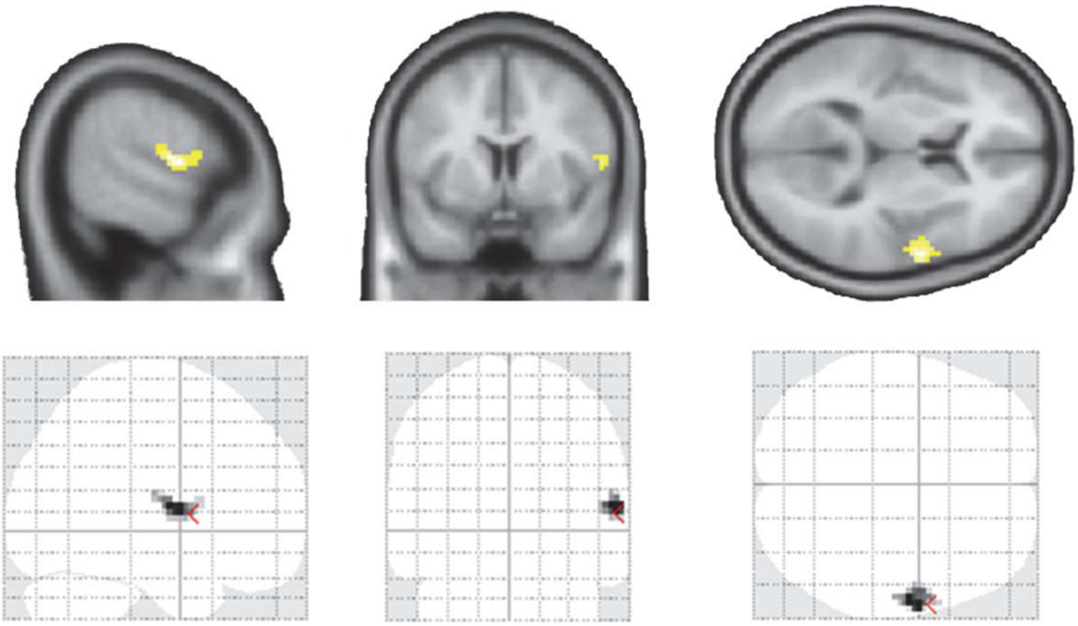

Figure 15. Group differences in connectivity patterns linked to laughter type differences - comparing activation patterns to taunting laughter to joyful laughter (TD (TAU > JOY) > ASD, (TAU > JOY)); PPI analysis using the right amygdala as a seed region. An increase in connectivity between the right amygdala and the right frontal lobe, precentral gyrus and the superior temporal gyrus could be observed. Above, the area exhibiting an increase towards the right amygdala is superimposed on a mean anatomical image, below, it is depicted in a transparent outline of the brain. Local maximum x: 57, y: -6, z: 12, minimal cluster extent 66 voxel.

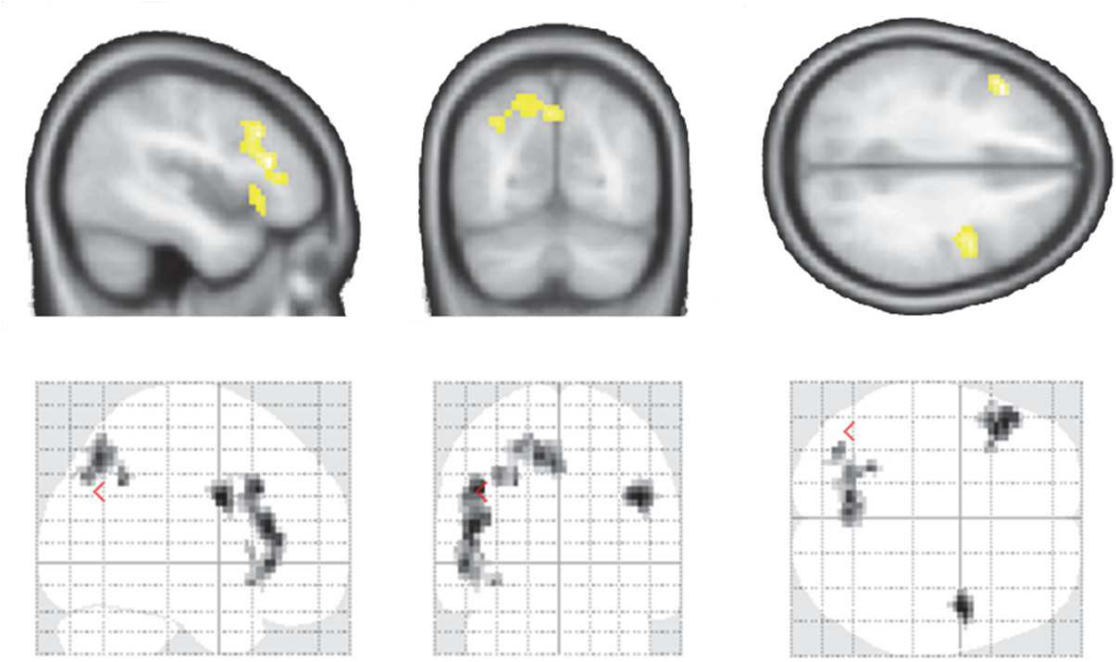

Figure 16. Group differences in connectivity patterns linked to laughter type differences - comparing connectivity patterns in response to joyful laughter to connectivity patterns in response to taunting laughter (TD (JOY > TAU) > ASD (JOY > TAU)), PPI analysis using the right FFA as a seed region. In this PPI analysis, an increased connectivity between the right FFA and the right inferior frontal gyrus and precentral gyrus (local maximum x: 45, y: 3, z: 30), the right FFA and left inferior frontal gyrus (local maximum x: -48, y: 27, z: 15), as well as between the right FFA and the left parietal lobe and the precuneus was found (local maximum x: -9, y: -66, z: 48). In the upper part of the figure, the areas with a higher connectivity to the right FFA are superimposed on a mean anatomical image, in the lower part, they are visualized in a transparent outline of the brain. Minimal cluster extent 61 voxel.

Table 9. PPI analyses results - Regions exhibiting decreased relative connectivity with previously defined regions of interest.

Group comparison TD > ASD	x	Y	z	Z-score	Cluster size (voxel)
Contrast Main ALL					
left TVA[1] ➡ middle frontal gyrus	-33	36	24	4.87	92
left TVA[1] ➡ middle occipital gyrus	21	-81	15	4.49	112
left TVA[1] ➡ left parietal lobe, precuneus, brodmann area 7	-18	-51	57	4.10	139
left TVA[1] ➡ left limbic lobe, cingulate gyrus	-6	6	36	3.96	87
Contrast TAU[3] > JOY[4]					
right amygdala ➡ right frontal lobe, precentral gyrus, superior temporal gyrus	57	-6	12	4.03	68
Contrast JOY > TAU					
right FFA[2] ➡ right inferior frontal gyrus, precentral gyrus	45	3	30	3.99	70
right FFA[2] ➡ left inferior frontal gyrus	-48	27	15	3.91	242
right FFA[2] ➡ left parietal lobe, precuneus	-9	-66	48	3.77	190

1 TVA - temporal voice area, 2 FFA - fusiform face area, 3 TAU - socially excluding laughter, 4 JOY - socially including laughter.

3.4. Summary of results

In the analysis of questionnaires, subjects with ASD exhibited significant higher gelotophobia and lower gelotophilia scores than TD controls. Also, a higher social anxiety, as determined by the LSAS, was observed for ASD individuals. They reported higher social anxiety and avoidance, and subsequently had a higher total score as well. This difference was significant in all domains (for the score measuring anxiety and for the total score). Significant differences were also found in respect to depressive symptoms as well as social initiation and emotional support.

In the analysis of behavioral data, a significant difference in the rating of friendly or joyful laughter could be observed between the ASD group and the control group, as ASD subjects rated friendly laughter as less socially including as compared to TD controls. Furthermore, the difference in ratings of social inclusiveness of the laughter type presented were significantly smaller between friendly and taunting laughter in the ASD group as compared to controls.

In the analysis of the audio-visual social perception experiment, hemodynamic changes in all ROI (bilateral amygdala, FFA, TVA, and the right pSTS) could be observed. Not all clusters reached significance at a whole brain level, presumably due to small sample size, but all activation clusters were significant when subjected to a small volume analysis (Table 6, Figure 10). There were no differences in activation between both groups. In the PPI-analysis, a reduction in connectivity between nodes of the social perception network and frontal brain areas could be observed in the ASD group. Specifically, connectivity was reduced between the left TVA and the superior and medial frontal gyrus during the presentation of human voices.

Also, connectivity between the left TVA and medial frontal gyrus and the limbic lobe, and between the right TVA and the frontal lobe, anterior part of caudate and limbic lobe, respectively, exhibited a negative correlation with AQ scores during the presentation of human voices as compared to other sounds.

In the laughter perception experiment, TD controls showed more activation in the left IFG than ASD subjects in response to all laughter in general. TD controls also exhibited a higher connectivity than ASD subjects between the left TVA and the MFG, MOG, and parietal and limbic brain regions under this condition (across all laughter types (Main ALL)). Furthermore, in comparison to the ASD group, TD controls showed an increase in connectivity between the right amygdala and the STS and frontal brain regions in response to taunting laughter rather than friendly laughter, and between the right FFA and the bilateral IFG and the precuneus, when the activation response to friendly laughter was contrasted against the activation response to taunting laughter.

4. Discussion

4.1. Discussion of results

„Over the course of the past years, several theories have been put forward as to what the neural correlates of social interaction difficulties in autism might be[18]. The two most important theories state an altered activation pattern in regions relevant for the processing of socially relevant stimuli (especially a hypoactivation in ASD, as found by Critchley et al., 2000; Dalton et al., 2005; Watanabe et al., 2012) or an underconnectivity between those regions (Belmonte, Allen, et al., 2004; Welchew et al., 2005). So far, findings have been rather inconclusive as there are a number of studies reporting results that are supportive of either hypothesis.“

Our study was aimed at investigating behavioral differences between TD controls and ASD subjects, differences in cerebral activation patterns, and connectivity changes in autism, using two different experimental approaches: The first experimental setup investigated the processing of implicit social cues. Moreover, the second setup addressed the perception and explicit judgment of laughter as an important multi-modal communicative social signal, analyzing behavioral differences as well as associated changes in cerebral activation and connectivity. For clarity, the results of both experiments will first be discussed separately, followed by a comprehensive discussion.

- Behavioral differences in response to laughter

In the rating of laughter types, friendly-joyful laughter was rated significantly less socially inclusive by ASD subjects. This might be interpreted tentatively as a negative interpretation bias ASD subjects might have even towards friendly laughter, as they yielded significantly higher scores for gelotophobia in the PhoPhiKat questionnaire. Also, a significant smaller difference between the mean rating of social inclusiveness of joyful and taunting laughter was observed between groups. This might be construed as a less clear differentiation of

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laughter types by ASD subjects - i.e. as ASD subjects having more difficulty with differentiating between friendly-joyful and taunting laughter. Because of marked gelatophobia and difficulties in differentiating between laughter types, ASD subjects might therefore be rating all expressed laughter as less socially inclusive. These behavioral differences in the evaluation of a non-verbal multimodal social stimulus are in line with ASD diagnostic criteria that emphasize behavioral difficulties people with ASD experience in social situations.

- Processing of implicit emotional cues

In the audio-visual perception experiment, „we found no differences in the magnitude of hemodynamic responses, neither in the FFA nor in the TVA, in contrast to previous experiments reporting hypoactivation for both regions in ASD (compare, for example, for the FFA (Pierce et al., 2001; Schultz et al., 2003), and for the TVA (Gervais et al., 2004))[19]. Therefore, studies with a larger sample-size would be needed to resolve the issue of altered activation patterns in FFA and TVA in ASD, as potentially the relatively small effect size (please compare Tables 1 and 2) might explain the differences between previous studies. Furthermore, at least one study (featuring 16 ASD patients) did not find differences in activation of the TVA in ASD patients while listening to voices (Schelinski, 2014) and there are other studies that found no activation deficit in the FFA (Hadjikhani et al., 2004).

However, we observed a reduction in connectivity, namely between the left TVA and frontal brain areas (medial and superior frontal gyrus). These frontal brain areas are known to be involved in higher-order mental processes like mentalizing and reward-anticipation that are pivotal for social interaction (Amodio et al., 2006). Our findings are in concordance with other studies reporting impaired connectivity in ASD (Baron-Cohen, Ring, et al., 1999; Ashwin et al., 2007; Wicker et al., 2008). Moreover, we also showed that connectivity

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was negatively correlated with AQ scores. However, even if the results of our study are supportive of the underconnectivity hypothesis in ASD patients, underconnectivity might not be the only mechanism underlying this disorder.

More recently, a third theory regarding neural correlates of autism has been proposed (Courchesne et al., 2005; Maximo et al., 2013), stating that autism might be linked to local overconnectivity. This hypothesis is not as contradictory to the theory of underconnectivity as it seems. In fact, both theories are compatible as overconnectivity on a global scale might be correlated with a relative reduction in connectivity between regions that usually, in TD controls, exhibit a strong connection. For example, Lee et al. found, no difference in connectivity between ASD and TD children at a young age (Lee et al., 2009). However, they also found that connectivity changes emerged with the progression of time, resulting in an underconnectivity in ASD children. Therefore, a possible explanation for this phenomenon could be the observation that, during neural development in TD persons, connectivity between brain regions of functional networks is strengthened with age (e.g., (Uddin et al., 2011). It seems that important connections are fostered and get strengthened consecutively whereas other connections that are not used wither and vanish, which results in a specialization towards relevant processes. A failure of this selection process in ASD could result in a long-range under- and local overconnectivity. Local overconnectivity preponderating over long-range underconnectivity could result in total increase in connectivity on whole-brain scale, which could result in a poorer specialization towards certain tasks. This might be a possible explanation for the difficulties of ASD individuals in social situations that are easy to master for most TD individuals. However, there are few longitudinal neuroimaging studies investigating the development of connectivity of children and adults with ASD, so more research is needed before assumptions about the relationship between changes in connectivity and behavioral characteristics in ASD can be made (for a review, please refer to (Maximo et al., 2014)).

One study that could shed light on the seemingly contradictory findings regarding connectivity in individuals with ASD has been put forward by Hahamy et al. (Hahamy et al., 2015). In their study, inter- and intrahemispheric connectivity was analyzed using resting state data of a large group of ASD subjects and TD controls. They found a pronounced variability in connectivity patterns in the ASD group. This pattern of heterogeneity, i.e. hypo- alongside hyperconnectivity, was distinctive in each ASD individual and, moreover, correlated to the severity of autistic traits. Therefore, heterogeneity seems likely to be the reason for discrepant findings in studies investigating connectivity in ASD individuals.“

- Processing of laughter as a multimodal non-verbal emotional cue

To my knowledge, until now no study has focused specifically on the perception and cerebral processing of different laughter types in ASD.

In this experimental set-up, a higher activation was found in the left IFG in the TD group in response to all laughter types (Main ALL), compared to the ASD group. The left IFG has been shown to be involved in processes including retrieval of semantic knowledge, reading the mind in the eye task as well as empathy. Several studies outline the involvement of the bilateral inferior frontal cortex in the explicit evaluation of emotional prosody (Ethofer et al., 2006; Ethofer et al., 2012, (Wildgruber et al., 2006; Bruck et al., 2011)) However, no difference in activation in the right IFG was observed. Taken together, this finding could indicate that TD individuals exhibit more activation in brain regions related to empathy when being presented with laughter than ASD individuals. This might be due to a lack of attention to social cues or attention to different aspects of social cues in ASD individuals. Also, this difference in activation might be due to a difference in the degree of empathic evaluation of social cues between the two groups.

In the PPI analysis, TD controls exhibited a higher connectivity between the left TVA and several other regions in response to all laughter types (Main ALL): the MFG, left precuneus and the cingulate cortex. This suggests a stronger association in the TD group as compared to ASD individuals between an area of human voice perception (i.e. the TVA) and mentalizing regions when listening to laughter in general. This is also corroborating the results of the study by

Wildgruber et al. (Wildgruber et al., 2013), who found an increase in connectivity between auditory association areas and frontal brain regions involved in mentalizing tasks when listening to complex social laughter types. Connectivity was also increased towards visual associative areas - the middle occipital gyrus - and the left parietal lobe. The middle occipital gyrus is part of the secondary visual cortex, that aides visuospatial information processing and is also activated during attention to emotion in visual processing (Haxby et al., 1991; Goodale et al., 1992; Lane et al., 1999), as needed for the processing for the audiovisual cues presenting laughter in our experimental setup. The left parietal cortex, on the other hand, serves several cognitive functions, including affective working memory, memory of one‘s own experiences, and attention to visual cues (likewise needed for processing video stimuli; Tulving et al., 1994; Jovicich et al., 2001; Rama et al., 2001; Caplan et al., 2006). Taken together, these findings might reflect the processes associated with the perception and interpretation of laughter in general (regardless of observer perspective) - making inferences about the mental state of the person laughing, higher order visual processing, autobiographic memory, and working memory.

The contrasts of individual laughter types yielded further changes in connectivity: When connectivity patterns in response to taunting laughter were contrasted with those in response to friendly-joyful laughter, TD controls showed an increase in connectivity between the right amygdala (involved in processes of judging emotional salience (Phelps et al., 2005)) and the right frontal lobe, inferior precentral gyrus, and right STG. The right frontal lobe plays a role in the shifting of attention towards an important cue and in inhibition and attention control (Hampshire et al., 2010), possibly implicating that the perception of taunting laughter, that is perceived as being socially exclusive, causes a shift of attention towards this negative, emotionally salient stimulus. Furthermore, the increased connectivity towards the right STG - that serves the explicit appraisal of emotional prosody (Ethofer et al., 2006; D. Wildgruber et al., 2006; Ethofer et al., 2012) - might imply an importance of the evaluation of prosodic properties and reliance on acoustic information during the perception and interpretation of taunting laughter. The connectivity towards the inferior precentral gyrus, the motor region controlling movements of the larynx, mouth and tongue and involved in the production of „voluntary“ laughter (Wild et al., 2003), might reflect the „mirror system“ underlying the contagiousness of laughter. Interestingly, this connectivity was not found for any of the other laughter types, although contagiousness is not limited to taunting laughter (which is perceived as a socially excluding laughter). A - very tentative - hypothesis might be that it could be more important to join into taunting laughter rather than other laughter types, as an attempt to abate its ostracizing effect and to reassert group membership. In the contrast condition (JOY > TAU), TD subjects showed an increase in connectivity between the right FFA, a region responsive to visual cues (i.e. faces (Haxby et al., 2000)) and the right and left IFG (associated with the retrieval of semantic information and the explicit evaluation of socially important cues in nonverbal communication (Poldrack et al., 1999)) and the left precuneus, indicating an importance of visual cues (facial expression) along with attention direction, semantic information retrieval, and mentalizing for the interpretation of friendly, socially including laughter.

However, no interaction between task and groups could be observed in the mentalizing task, where participants were asked to take on different observer perspectives. Thus, the mental differentiation between laughter directed at oneself (SELF) and directed at somebody else (OTHER) was not reflected by differences in activation patterns between the groups. Here, we had expected to find activation differences between ASD subjects and TD controls in areas involved in ToM tasks, but no significant difference could be found.

Taken together, the results of both experiments and the analysis of behavioral data corroborate current hypotheses regarding the neural mechanisms underlying autism. The analysis of behavioral data showed a marked gelotophobia, an, albeit not significant, increase in reaction time, a more negative rating of socially including laughter, and less differentiation between socially including and socially excluding laughter types, possibly reflecting a negative bias to laughter in general and difficulties in interpreting the assumed intention of the perceived laughter. These findings are also reflected in the findings of the image analysis. In response to laughter in general, ASD subjects showed less activation in the left IFG than TD controls - a possible neural correlate to the reduced ability to differentiate different laughter types in ASD. This is underpinning other findings of hypoactivation as a possible neural correlate to difficulties people with ASD experience in social situations. Also, changes in connectivity were observed, supporting previous studies which consistently found altered connectivity patterns in ASD individuals. During the implicit perception of social cues, ASD individuals exhibited a reduction in connectivity between important nodes of the social perception network, namely the temporal voice area, and frontal brain areas. Furthermore, this reduction in connectivity was negatively correlated with the severity of autistic symptoms as determined by the autism questionnaires.

Taking into account other recent studies on heterogeneity, the ostensible inconsistencies between changes we observed both in regard to the connectivity at the neural level and to the changes at the behavioral level in response to different laughter types and the fact that in some analyses, no differences between groups were found (no task-related differences in ratings between groups, only modest increase in reaction time in the ASD group) might be reconciled - while TD individuals exhibit consistent and comparable connectivity patterns, persons with ASD develop highly variable, but at the individual level permanent and stable patterns of connectivity (Hahamy et al., 2015). When analyzed at a group level, the averaging of these individual patterns might result in a mean that misrepresents the variability of idiosyncratic connectivity patterns. Apparently, this individual pattern could enable ASD individuals to perform emotional tasks and mentalizing processes to a certain degree, especially in high functioning individuals and when explicitly paying attention. It seems that people with ASD need - and are able - to learn in which context to pay attention to social signals and have to actively shift their attention towards them, whereas typically developed controls look out for potentially relevant signals whenever they see a human face, listen to voices, or encounter laughter. Because of differences at a neural level, people with ASD might find it harder to make those inferences in a social context and feel less confident in their judgments. Indeed, their ability to compensate might be limited, as the behavioral and neural differences found between the ASD and the TD group in the perception and interpretation of different laughter types, i.e. highly complex and multimodal stimuli, might suggest. the correct interpretation of complex social laughter types - that can convey different intentions and mental states and are frequently used as communicative tools - might be difficult. In turn, these difficulties might lead to feelings of insecurity, gelotophobia, social anxiety, problems in engaging with others, and, ultimately, depressive symptoms.

4.2. Limitations of the study

There are some limitations to our study design, as between both experiments, there were some methodological differences: The psychological variables for the PPI analysis, that in both cases corresponded to the chosen contrasts, varied between experiments - on the one hand contrasting different affective emotional stimuli with each other, and contrasting social cues with neutral stimuli on the other hand.

In the analysis of behavioral data, there were only few differences between both groups, contrary to what we had expected. Apart from possibly indicating a good adaptation of ASD subjects, this might also be explained by the relatively small sample size in both groups, as the effect size was small (please compare Tables 1 and 2).

This small sample size might also be the reason that we found only one statistically significant difference in activation between both groups in the image analysis. Moreover, within the scope of the current study it is not possible to determine whether the social interaction difficulties in ASD give rise to the changes in neural networks or whether this is a process that happens vice versa[20]. The results, however, do corroborate the association between hypoconnectivity of specific regions involved in the processing of socially relevant stimuli […]. In our study, we chose psycho-physiological interaction

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[20] All following paragraphs that are highlighted with underscore and indicated with quotation marks have been cited verbatim from (Hoffmann et al., 2016). Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Journal of Neural Transmission, 123(8), 937-947. Reduced functional connectivity to the frontal cortex during processing of social cues in autism spectrum disorder. Hoffmann, E., Bruck, C., Kreifelts, B., Ethofer, T., & Wildgruber, D. Springer Vienna (2016). https://link.springer.com/journal/702

analyses for determining connectivity. However, this PPI analysis approach is not well-suited for analyzing global connectivity, as it requires the definition of a seed region and determines connectivity only with respect to this selected seed region. Also, some ROIs were very small and did not reach significance at whole brain level, which might have had an impact on the ensuing activation and PPI analyses. [...] In the light of recent studies it would have been interesting to test our data sets for heterogeneity in ASD subjects, although small sample size hindered this analytical step. However, this might be an interesting approach for future studies.“

4.3. Conclusion

The limitations of the study notwithstanding, „the […] reduction in connectivity between regions involved in the processing of socially relevant cues“ in the audio-visual social perception experiment „is in line with findings by recent studies on regions of the social perception network in ASD (such as the TVA or the amygdala). Furthermore, we found a correlation between the severity of autistic symptoms as determined by the AQ and the reduction in connectivity. This is not only reflecting the spectrum character of ASD but also indicating the significance changes in connectivity may be linked to autistic traits, thus corroborating prevailing theories on potential neural correlates in ASD.“

These theories on the possible neural correlates underlying autism are further supported by our findings of the social laughter experiment, Here, differences at the neural level were observed in the ASD group, where a hypoactivation and a reduction in connectivity compared to the TD group was found within and between important nodes of the social perception network associated with theory of mind processes in response to laughter stimuli. Moreover, these changes at the neural level corresponded with behavioral data, which demonstrated that ASD subjects differentiate less clearly between different laughter types and rate laughter overall as more socially exclusive than TD controls.

The findings in our study give new and interesting insights into the perception and neural integration of both explicit and implicit social stimuli as well as the interpretation of different complex social laughter types as a multimodal, non-verbal social communicative stimuli, both in ASD subjects and TD controls.

5. Summary

In social situations, the perception and correct interpretation of social and emotional cues is vital for interaction, group formation, and the perpetuation of relationships. This social interaction, however, is a highly complex cognitive task that requires the integration of several different mental processes and, thus, involves many brain regions and neural networks. In autism spectrum disorder, this complex interaction is impaired - ASD is associated with difficulties in socializing and the interaction with others, not seldomly causing distress and isolation in those affected. In our fMRI study, we sought to elucidate how social cues are perceived and processed at the neural level in ASD as compared to TD controls, using two experimental set-ups. The data sets of both experiments were analyzed for group differences in activation patterns and changes in connectivity, as determined by a PPI-analysis approach (comparing 9 ASD subjects with 9 TD controls).

In the audio-visual social perception experiment, we investigated the implicit processing of social cues, i.e. faces, human voices, and combined audiovisual cues. Emphasis in the analyses was laid on important nodes of the social perception network - the amygdalae, the bilateral TVA and FFA, and the right pSTS. Those regions were defined as ROIs for the ensuing image analyses. Both activation patterns in as well as connectivity between those regions was analyzed.

The social laughter perception experiment focused on the explicit evaluation of social cues, using laughter as a salient social signal. The perception of distinct types of laughter (tickling laughter, joyful laughter and taunting laughter) was investigated. Laughter is a complex, non-verbal multimodal social signal, that exhibits prosodic characteristics, serves the initiation of reciprocal relationships and the formation of larger groups, and can convey different mental states and intentions. As laughter is such an important communicative tool, we expected this study might shed light on the perception of social cues in ASD individuals - which, to our knowledge, has not been studied using distinct types of laughter before. Additionally, questionnaires were conducted to determine e.g. gelotophobia in ASD or the AQ score in TD controls.

In the analysis of the audio-visual social perception experiment, stimulus-specific hemodynamic changes in all ROIs mentioned above could be observed. However, there were no differences in elicited activation between both groups. In the PPI-analysis, a reduction in connectivity between the left TVA and frontal brain areas could be observed in the ASD group. Furthermore, under this condition, connectivity between the left and right TVA and the frontal lobe exhibited a negative correlation with AQ scores.

In the laughter perception experiment, TD controls showed more activation in the left IFG than ASD subjects in response to laughter in general. TD controls also exhibited a higher connectivity than ASD subjects between the left TVA and the MFG, MOG, and parietal and limbic brain regions under this condition. Furthermore, in the explorative analysis of different laughter types, TD individuals showed a higher connectivity in comparison to the ASD group between the right amygdala and frontal and temporal brain regions in response to socially excluding laughter, as compared to socially including laughter, and, furthermore, between the right FFA and the bilateral IFG and the precuneus, when being presented with socially including laughter as compared to taunting laughter. As expected, ASD subjects showed higher scores for gelotophobia, depressive symptoms, and social anxiety in the analysis of the questionnaires than the participants in the control group.

The findings in both experiments corroborate current theories of ASD that propose that differences in activation patterns as well as a change in connectivity between important nodes of the social perception network and frontal brain areas - that are involved in higher-order cognitive processes - might be the neural substrate of observed difficulties in social interaction in autism. Those changes in connectivity were observed both during the explicit and the implicit perception of social cues. Furthermore, changes in connectivity were positively correlated with the severity of autistic symptoms and corresponded to differences in the analysis of behavioral data. Therefore, this study contributes relevant data regarding cerebral activation patterns and connectivity during the perception of implicit social cues and laughter in people with autism spectrum disorder as well as in typically developed controls.

6. German Summary - Deutsche Zusammenfassung

Übersicht über Autismus Spektrum Störungen und Ziele der Studie

Als Autismus beschreibt man laut dem Diagnostic and Statistical Manual of Mental Disorders (DSM-V) eine „tiefgreifende Entwicklungsstörung“. Aktuell werden fünf, vormals verschiedene, Diagnosen unter dem Begriff Autismus Spektrum Störung (ASD) zusammengefasst. Dabei ist die Bandbreite der präsentierten Symptome groß und ihre Ausprägung bzw. die Einschränkungen, die betroffene Personen erleben, individuell sehr unterschiedlich. Allen Betroffenen gemeinsam sind Auffälligkeiten in drei Hauptbereichen: Schwierigkeiten in der sozialen Interaktion, auf verschiedene Weise beeinträchtigte Kommunikation und schließlich Verhaltensmuster, die sich in Stereotypien, repetitiven Verhaltensmustern oder in Tiefe und Art ungewöhnlichen Interessen und Beschäftigungen äußern können. Darüber hinaus besteht bei ASD eine hohe Komorbidität mit anderen psychiatrischen Erkrankungen, wie z.B. Depressionen.

Insbesondere die Schwierigkeiten in der sozialen Interaktion mit anderen werden oft als belastend empfunden und können hohen Leidensdruck bei den Betroffenen verursachen. ASD Patienten können u.a. nur schwer vom Gesichtsausdruck oder der Prosodie auf die Gefühlslage eines Gegenübers schließen, sie vermeiden Augenkontakt und das Initiieren und die Aufrechterhaltung von sozialen Kontakten fallen ihnen schwerer als Vergleichspersonen.

Es existieren verschiedene Theorien darüber, worin die neurologischen Korrelate der sozialen Interaktionsschwierigkeiten bestehen könnten: Zum Einen werden Aktivierungsunterschiede in Hirnregionen, die bei der Verarbeitung sozialer Signale eine Rolle spielen, angenommen, zum Anderen gerät zunehmend die Untersuchung der Verbindung dieser Regionen untereinander in den Fokus der Forschung. Mehrere Studien fanden bei Autisten eine Hypoaktivierung in den Amygdalae und dem fusiformen Gyrus. Bei Untersuchungen der Konnektivität fanden Studien sowohl eine erhöhte als auch eine reduzierte Konnektivität zwischen an der Verarbeitung von sozialen Signalen beteiligten Hirnregionen. Außerdem fanden sich Hinweise, dass das

Konnektivitätsmuster bei Autisten individuell sehr unterschiedlich, aber intrapersonell konstant sind - dies wird als Idiosynkrasie bezeichnet.

Ziel unserer fMRT-Studie war es, die Aktivierung von Hirnregionen, die an der Wahrnehmung und Verarbeitung sozialer Signale beteiligt sind, zu untersuchen. Der erste Teil der Experimente diente der Identifizierung von Strukturen, die durch die Verarbeitung menschlicher Stimmen, Gesichter und audiovisueller Integration aktiviert werden. Im Fokus lagen dabei die rechte und linke Amygdala, der rechte und linke fusiforme Gyrus, die rechte und linke temporale Sprachregion und ein audio-visuelles Integrationsareal im rechten posterioren superioren temporalen Sulcus. Untersucht wurden Aktivierungsunterschiede während der impliziten Wahrnehmung und Verarbeitung von sozialen Signalen zwischen den Gruppen der Autisten und der neurotypischen Kontrollen. Außerdem wurde eine Konnektivitätsanalyse mit den oben genannten Regionen als Ursprungsregionen durchgeführt. Zudem erfolgte eine Korrelation der Aktivierung und neuronalen Konnektivität mit den Werten des AQ, eines Fragebogens, der die Stärke der Ausprägung autistischer Charakterzüge untersucht.

Im zweiten Teil der Studie wurde die Verarbeitung von verschiedenen Lachtypen als nonverbale, audiovisueller Signale untersucht. Außerdem wurden die Probanden mit einem Mentalizing-Task instruiert. Hierbei wurden die Probanden gebeten, mental unterschiedliche Perspektiven einzunehmen - in der einen Kondition sollten sie sich vorstellen, sie selbst seien der Adressat des beobachteten Lachens, und in der anderen Kondition, sie beobachteten eine Schauspieler beim Einüben unterschiedlicher Lachtypen. In diesem experimentellen Teil wurden Aktivierungs- und Konnektivitätsunterschiede zwischen den Gruppen - in Bezug auf Lachtyp und Beobachterperspektive - sowie behaviorale Daten analysiert.

Material und Methoden

Analysiert wurden die Verhaltensdaten zweier in Bezug auf Geschlecht, Alter, IQ und Bildungsgrad vergleichbarer Gruppen à 10 Teilnehmern (Autisten vs. Kontrollprobanden). Nach Ausschluss nicht zu verwertender Datensätze lag die

Gruppengröße für die Analyse der MRT-Datensätze beider Gruppen (Autisten - ASD und neurotypische Kontrollen - TD) bei 9 Teilnehmern (n (gesamt) = 18).

Fragebögen

Alle Teilnehmer füllten mehrere Fragebögen aus: Den AQ (autism questionnaire), der die Ausprägung autistischer Symptome erfragt, das Beck Depressions Inventar zur Abfrage depressiver Symptome, den PhoPhiKat zur Einschätzung der Ausprägung von Gelotophobie (Angst davor, ausgelacht zu werden), Gelotophilie (Freude daran, ausgelacht zu werden) und Katagelastizismus (Freude am Auslachen anderer), den Interpersonellen Kompetenz Fragebogen, einen Fragebogen zur Sozialen Angst und Vermeidung sowie einen Test zur emotionale Intelligenz (Mayer-Salovey-Caruso Emotional Intelligence Test). Die Fragebögen wurden statistisch ausgewertet und auf Gruppenunterschiede hin untersucht. Im Falle des AQ erfolgte darüber hinaus eine Korrelationsanalyse mit den erhobenen fMRT-Datensätzen.

Identifizierung der an der Verarbeitung sozialer Signale beteiligten Hirnregionen

Zur Identifizierung der Hirnregionen, die an der Verarbeitung (impliziter) sozialer Signale beteiligt sind, wurden drei verschiedene Experimente durchgeführt.

1) Identifizierung von Gesichts-verarbeitenden Regionen: In diesem Experiment wurden den Probanden mehrere Blöcke visueller Stimuli präsentiert, die jeweils Bilder von Gesichtern, Häusern, Landschaften oder Alltagsgegenständen zeigten. Um die Aufmerksamkeit der Probanden zu erhöhen, wurden sie instruiert, bei direkter Wiederholung eines Bildes eine Taste zu drücken.
2) Identifizierung von Stimm-verarbeitenden Regionen: Um die Stimm-verarbeitenden Regionen zu identifizieren, wurden den Teilnehmern in diesem Experiment auditive Stimuli vorgespielt. Menschliche Stimmen, Tierlaute und Umweltgeräusche wurden jeweils in eigenen Blöcken präsentiert. Dieses Experiment wurde als passive Aufgabe durchgeführt, daher wurden hierfür keine Verhaltensdaten gesammelt.

3) Identifizierung von Regionen, die an der Integration audiovisueller Signale beteiligt sind: In diesem Experiment wurden kurze Videoclips präsentiert, in denen Schauspieler kurze deutsche Wörter mit unterschiedlichem Unterton (z.B. neutral, ängstlich, angeekelt) sprachen. Dabei wurde nur der Kopf der Schauspieler gezeigt. Die Clips wurden auf drei verschiedene Arten vorgespielt: Videos mit Tonspur, stumme Videos und Tonspur ohne Videos. Um die Aufmerksamkeit der Teilnehmer zu erhöhen, wurden sie gebeten, beim jeweils zweiten Auftauchen eines Mannes eine Taste zu drücken.

Experiment zu Untersuchung der Verarbeitung von unterschiedlichen Lachtypen

Ziel dieses Teils der Studie war die Analyse der expliziten Wahrnehmung und der Verarbeitung von Lachen als eines nonverbalen, audiovisuellen Signals. Drei verschiedene Arten von Lachen (Kitzellachen, freudiges = sozial inkludierendes Lachen und höhnisches - sozial exkludierendes Lachen) wurden in Form 60 kurzer Videoclips von Schauspielern präsentiert, wobei jeweils nur deren Gesichter gezeigt wurden. Nach jedem Clip wurden die Probanden aufgefordert, auf einer vierteiligen Skala einzuordnen, wie sie das präsentierte Gelächter empfanden. Dabei konnten sie zwischen ANLACHEN und AUSLACHEN sowie zwischen jeweils geringer und starker Ausprägung wählen (ein Beispiel der Skala ist in Abbildung 5 dargestellt).

Der Block mit 60 Lachstimuli wurde zweimal hintereinander gezeigt, wobei den Probanden jeweils zwei verschiedene Instruktionen gegeben wurden. Die Teilnehmer wurden gebeten, sich bei der Betrachtung des Gelächters gedanklich in verschiedene Beobachterpositionen (entweder Adressat des Gelächters oder Betrachter, der einen Schauspieler beim Üben beobachtet) hinein zu versetzen und die Einordnung des Gelächters jeweils aus der jeweiligen Position heraus zu beurteilen.

Die Reihenfolge der Videoclips, die Orientierung der Skala sowie die Reihenfolge der Instruktion zur Beobachterperspektive wurden gleichmäßig über alle Probanden balanciert.

Analyse der fMRT-Daten: Aktivierungs- und Konnektivitätsanalyse

Die Analyse der MRT-Daten erfolgt mit Hilfe des Programmes SPM 8 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Aus Übersichtsgründen werden hier nur die finalen Analyseschritte erläutert, für eine genauere Darstellung der technischen Details und der Preprocessing-Schritte siehe Abschnitt 2 - Materials and Methods.

Die ersten drei Experimente dienten der Identifizierung Stimm-, Gesichts- und audiovisuell integrativer Areale. Dabei wurden die folgenden Kontraste berechnet:

1) FACES > HOUSES, OBJECTS, LANDSCAPES
2) VOICES > ANIMALS, ENVIRONMENT
3) AV > V, AV > A und eine Konjunktion AV > V UND AV > A, die mit Hilfe einer minimal t-Statistik berechnet wurde.

In die Berechnung der Kontraste wurden die Datensätze beider Gruppen mit einbezogen. Aufgrund eines Problems in der Datenaufzeichnung konnten bei der Analyse des audiovisuellen Integrationsareals nur 16 Datensätze ausgewertet werden. Hierbei zeigten sich Aktivierungen in den erwarteten Arealen. Mit Hilfe eines anatomischen Labeling-Tools wurde die korrekte anatomische Lage der Aktivierungen überprüft und eine small volume correction Analyse durchgeführt. Alle Areale waren in dieser Analyse signifikant.

Die identifizierten Bereiche wurden als Regions of Interest definiert, und als Ursprungsregion für die folgende Konnektivitätsanalyse und für die Analyse des zweiten Teils der Studie definiert.

Im nächsten Schritt erfolgte ein Gruppenvergleich (TD vs. ASD), um mögliche Gruppenunterschiede zu identifizieren sowie eine Korrelation der Aktivierung mit den AQ-Werten (CorrAQ).

Für die Konnektivitätsanalyse wurde der Ansatz der Psycho-Physiologischen-Interaktionsanalyse (PPI-Analyse) gewählt. Hierbei wird eine Region als Ursprung definiert und alle restlichen Hirnbereiche auf eine Koaktivierung mit der Ursprungsregion hin untersucht (detailliert erläutert in Abschnitt 2).

Analyse des Lachexperiments

Für die Analyse des Experiments, in dem die Verarbeitung verschiedener Lachtypen untersucht wurde, wurden mehrere Kontraste berechnet: Main ALL, Main JOY, Main TIC, Main TAU, Main SELF, Main OTHER, sowie komplexe Kontraste (siehe Abschnitt 2).

Für alle diese Kontraste wurde ein Gruppenvergleich in Bezug auf Aktivierungsunterschiede durchgeführt. Die Verhaltensdaten - die Bewertung der Lachtypen unter zwei verschiedenen Instruktionen - wurden ebenfalls auf Gruppenunterschiede, Unterschiede nach Lachtyp und instruierter Beobachterperspektive hin untersucht.

Ergebnisse

Ergebnisse der Fragebögen

Es zeigten sich höhere BDI-Werte in der Gruppe der Autisten, von denen mehrere bereits mit Depressionen diagnostiziert waren. Außerdem zeigten sich in der ASD Gruppe höhere Gelotophobie-Werte sowie kleinere Werte in der Kategorie Gelotophilie. Auch die Werte des LSAS, der Angst und Vermeidungsverhalten in sozialen Situation erfasst, waren in der Gruppe der Autisten signifikant höher.

(Für die detaillierten Analyseergebnisse der Fragebögen siehe Abschnitt 3).

Analyse der Verhaltensdaten

In der Analyse der Verhaltensdaten zeigte sich in der Gruppe der Autisten ein signifikanter Unterschied in der Beurteilung von sozial inkludierendem Gelächter. Hier zeigten sich geringere Werte als in der Kontrolle, d.h. dieses Gelächter wurde durch die Autisten als weniger inkludierend wahrgenommen, als durch die Kontrollprobanden. Auch die durchschnittlichen Ratings von sozial inkludierendem und exkludierendem Gelächter unterschieden sich zwischen den beiden Gruppen - in der Gruppe der Autisten zeigten sich eine signifikant geringere Unterscheidung zwischen beiden Gelächtertypen. In der Gruppe der Autisten zeigte sich darüber hinaus eine geringfügige, nicht statistisch signifikante Verlängerung der Reaktionszeit.

Aktivierungs- und Konnektivitätsanalyse

Die Ergebnisse der ersten Aktivierungsanalyse mit dem Ziel der Identifizierung Gesichts-, Stimm- und audiovisuell integrativer Areale sind in Tabelle 6 und Abbildung 10 dargestellt. Es zeigten sich Aktivierungen in der rechten und linken Amygdala, im rechten und linken fusiformen Gyrus, in der rechten und linken temporalen Stimmregion, und im Bereich des rechten posterioren superioren temporalen Sulcus.

Im Gruppenvergleich konnten keine Unterschiede der regionalen zerebralen Aktivierung und keine Korrelation der hämodynamischen Aktivierung mit AQ-Werten festgestellt werden.

In der PPI-Analyse zeigte sich eine Verminderung der Konnektivität bei Autisten im Vergleich zu TD-Kontrollen zwischen der linken TVA und dem superioren und medialen frontalen Gyrus.

Außerdem zeigte sich eine negative Korrelation zwischen dem AQ und der Konnektivität zwischen der rechten TVA und dem Frontallappen, dem Nucleus caudatus, dem Lobus limbicus und dem medialen frontalen Gyrus sowie zwischen der linken TVA und dem Lobus limbicus, dem anterioren Cingulum und dem medialen frontalen Gyrus.

Ergebnisse des Lachexperiments

Im Gruppenvergleich zeigte sich in der Kontrollgruppe eine höhere Aktivierung im Bereich des linken IFG im Kontrast Main ALL.

Im gleichen Kontrast fand sich eine erhöhte Konnektivität zwischen der linken TVA und dem MFG, MOG, linken Parietallappen und dem linken Gyrus cinguli gegenüber der ASD Gruppe

Im Kontrast JOY > TAU war die Konnektivität in der Kontrollgruppe zwischen der rechten FFA und rechtem IFG und prezentralen Gyrus sowie dem linken IFG, dem linken Parietallappen und dem Precuneus im Vergleich zu der Gruppe der Autisten erhöht.

Im umgekehrten Kontrast, TAU > JOY, zeigte sich in der Kontrollgruppe eine Erhöhung der Konnektivität zwischen der rechten Amygdala und dem rechten

Frontallappen, dem rechten prezentralen Gyrus und dem rechten STG gegenüber der Konnektivität in der Gruppe der Autisten.

Diskussion

In der aktuellen Autismusforschung gibt es verschiedene Theorien dazu, welche neuronalen Korrelate den von Autisten erlebten Schwierigkeiten in sozialen Situationen zu Grunde liegen könnten. Dabei sind die Studienergebnisse nicht einheitlich: Zum Einen finden sich Hinweise für Hypoaktivierungen in Hirnregionen, die an der Verarbeitung sozialer Signale beteiligt sind. Zum Anderen konzentrieren sich viele Studien zunehmend auf die Untersuchung der Konnektivität, wobei sich sowohl Hinweise für eine Hypokonnektivität finden, als auch Ergebnisse, die für eine Hyperkonnektivität sprechen.

In unserer Studie untersuchten wir sowohl Aktivierungsmuster als auch die Konnektivität zwischen Hirnregionen, die an der Verarbeitung sozialer Signale beteiligt sind. Dabei fanden sich im ersten experimentellen Teil keine Aktivierungsunterschiede zwischen der Gruppe der Autisten und der Gruppe der Kontrollprobanden. Jedoch zeigte sich eine Verminderung der Konnektivität zwischen der linken TVA und frontalen Hirnbereichen sowie eine negative Korrelation zwischen den AQ-Werten der Probanden und der Konnektivität zwischen der TVA beidseits und dem frontalen Kortex. Insbesondere die negative Korrelation mit dem AQ spiegelt hierbei den Spektrumcharakter, der sich bei ASD findet, wider. Der zweite Teil der Studie konzentrierte sich auf die Verarbeitung verschiedener Lachtypen als multimodaler, non-verbaler, vokaler und affektiver Stimuli. Hierbei zeigte sich im Kontrast Main ALL in der Kontrollgruppe eine erhöhte Aktivierung im linken IFG, einem Bereich, der mit Empathie und semantischem Gedächtnis assoziiert ist. Zudem war in diesem Kontrast die Konnektivität zwischen der linken TVA und verschiedenen Regionen erhöht, die an Mentalizing-Prozessen beteiligt sind.

Bei der Kontrastierung verschiedener komplexer sozialer Lachtypen zeigten sich in mehreren Kontrasten Veränderungen in der Konnektivität. In der Kontrollgruppe zeigte sich im Kontrast TAU > JOY eine erhöhte Konnektivität zwischen Regionen, die mit der Salienz emotionaler Signale und Prosodie assoziiert sind, während sich im Kontrast JOY > TAU eine erhöhte Konnektivität zwischen Gesichts-verarbeitenden Regionen und frontalen Hirnbereichen fand. Die Ergebnisse der Konnektivitätsuntersuchungen spiegelten sich auch in der Analyse der behavioralen Daten der beiden Gruppen wider. Hier zeigte sich in den gleichen Kontrasten, dass sozial inkludierendes Gelächter durch Autisten negativer bewertet wird als durch Kontrollprobanden und dass sie darüber hinaus weniger stark zwischen inkludierenden und exkludierenden Lachtypen differenzieren als Kontrollprobanden.

Einschränkungen der Studie und Ausblick

In der Analyse der MRT-Daten (nicht Ganzhirn-signifikante Aktivierungen) fanden sich Ergebnisse, die zwar eine statistische Tendenz aufwiesen, jedoch nicht das Signifikanzniveau von $p < 0.05$ erreichten. Auch zeigten sich statistisch signifikante Veränderungen der Konnektivität in der PPI-Analyse nur in Kontrasten, die eine große Ursprungsregion aufwiesen. Beides ist vermutlich auf die geringe Probandenzahl von $n = 9$ Autisten zurückzuführen. Daher wären weitere Untersuchungen mit einer größeren Probandenzahl von Vorteil, um die statistische Aussagekraft der Ergebnisse zu erhöhen. Auch eine Untersuchung der Heterogenität wäre mit einer größeren Stichprobe möglich.

Zusammenfassung

Die im ersten Teil der Studie gefundene Reduktion der Konnektivität bei der impliziten Verarbeitung emotionaler Stimuli entspricht aktuellen Forschungsergebnissen einer neuronalen Hypokonnektivität bei Autismus, wobei insbesondere die negative Korrelation mit dem AQ den Spektrumcharakter von ASD widerspiegelt.

Mit der Untersuchung der Verarbeitung von Gelächter wählten wir im zweiten Teil der Studie mit unterschiedlichen sozialen Gelächtertypen einen neuen Versuchsansatz und einen komplexen Stimulus, um die explizite Verarbeitung sozialer Signale bei Autisten zu untersuchen. Auch die hier beobachtete, im Vergleich zu der Kontrollgruppe relativ weniger stark und anders ausgeprägte Konnektivität entspricht aktuellen Studienergebnissen im Bereich der

Autismusforschung. Diese Unterschiede zwischen beiden Gruppen auf der Ebene der neuronalen Aktivierungs- und Konnektivitätsmuster entsprachen ebenfalls den Unterschieden in der Analyse der Verhaltensdaten zwischen beiden Gruppen, d.h. der differierenden Einschätzung des beobachteten Gelächters.

Möglicherweise erlauben die beschriebene Heterogenität und Idiosynkrasie der Konnektivitätsmuster Autisten bei explizit gerichteter Aufmerksamkeit eine vergleichsweise gute Beurteilung sozialer Signale, wohingegen die Verarbeitung sozialer Signale bei normal Entwickelten und „normalem“ Konnektivitätsmuster unabhängig von expliziter Aufmerksamkeit ablaufen könnte. Dafür sprechen auch die Ergebnisse des ersten Experiments, die bei implizierter Verarbeitung emotionaler Signale eine ausgeprägte Hypokonnektivität in der ASD Gruppe zeigte. In der Analyse des Lachexperiments zeigten sich jedoch in einigen Analysen Unterschiede sowohl auf der Verhaltens- als auch auf der neuronalen Ebene zwischen beiden Gruppen, sodass bei Autismus die Kompensationsmöglichkeit durch Idiosynkrasie der neuronalen Konnektivität bei der Wahrnehmung sozialer Signale beschränkt sein könnte. Insbesondere die Differenzierung unterschiedlicher sozialer Lachtypen, für die komplexe Theory of mind Prozesse notwendig sind, scheint hierbei eine große Herausforderung für Menschen mit Autismus darzustellen.

Allerdings sind weitere Untersuchungen notwendig, um diese Hypothese zu untermauern, insbesondere, da aufgrund der geringen Stichprobengröße keine Analyse der Heterogenität vorgenommen werden konnte. Hier bietet sich ein interessanter Ansatz für zukünftige Studien.

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8. Supplementary tables

Suppl. Table 1. Analysis of head movement with regard to group and experimental condition - first experimental setup -

	ASD		**TD**				
	mean	**SD**	**mean**	**SD**	**t-value**	**p-value**	**Cohen‘s d**
Experiment identifying face sensitive regions (n = 16)[1]							
x-translation	0.63	0.68	0.43	0.27	-0.78	0.04*	-0.39
y-translation	0.29	0.12	0.26	0.18	-0.43	0.73	-0.20
z-translation	0.83	0.63	0.72	0.41	-0.40	0.19	-0.21
x-rotation	0.01	0.01	0.01	0.01	0.87	0.55	0.00
y-rotation	0.01	0.01	0.01	0.01	0.22	0.60	0.00
z-rotation	0.01	0.01	0.01	0.00	-1.02	0.05*	0.00
Experiment identifying voice sensitive regions (n = 18)							
x-translation	0.48	0.26	0.23	0.15	-2.54	0.10	-1.18
y-translation	0.23	0.11	0.13	0.06	-2.33	0.15	-1.13
z-translation	0.74	0.31	0.46	0.26	-2.10	0.99	-0.98
x-rotation	0.01	0.01	0.01	0.01	-0.49	0.94	0
y-rotation	0.01	0.01	0.00	0.00	-0.90	0.50	0
z-rotation	0.01	0.00	0.00	0.00	-2.85	0.05*	infinite
Experiment identifying audiovisual integrative regions (n = 18)							
x-translation	0.46	0.36	0.21	0.09	-2.00	0.07(*)	-0.95
y-translation	0.25	0.13	0.17	0.12	-1.33	0.65	-0.64
z-translation	0.51	0.35	0.51	0.25	-0.04	0.62	0
x-rotation	0.01	0.01	0.01	0.01	0.59	0.71	0
y-rotation	0.01	0.01	0.00	0.00	-1.11	0.10	0
y-rotation	0.01	0.00	0.00	0.00	-1.27	0.54	0

*„Translational head movement reported in mm, rotational head movement in degree. 1 - One ASD subject showed excessive head motion, i.e. > 3 mm in one direction. Thus, this subject and one corresponding control were excluded from this condition, resulting in n = 16. * significant difference between groups. (*) trend level significant difference between groups.“* Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Journal of Neural Transmission, 123(8), 937-947. Reduced functional connectivity to the frontal cortex during processing of social cues in autism spectrum disorder. Hoffmann, E., Bruck, C., Kreifelts, B., Ethofer, T., & Wildgruber, D. Springer Vienna (2016).

Suppl. Table 2. Analysis of the behavioral data obtained in the experiments identifying face sensitive and audiovisual integration regions

	ASD		TD		t-value	p-value	Cohen‘s d
	hits	SD	hits	SD			
Recognition of a picture that was repeated immediately (one-back-task) during the experiment identifying face sensitive regions[1,2])	56.11	5.88	54.11	12.62	-0.43	0.08(*)	
Recognition of the second occurrence of an identical male voice within a block of stimuli during the audio-visual integration experiment - sound (A)[3,4,5]	7.33	3.67	8.00	2.24	0.47	0.29	
Recognition of the second occurrence of an identical male face within a block of stimuli during the audio-visual integration experiment - muted video (V)[3,4]	10.33	2.69	10.44	2.55	0.09	0.66	
Recognition of the second occurrence of an identical male face and voice within a block of stimuli during the audio-visual integration experiment - video with sound (AV)[3,4]	11.00	1.73	11.00	1.66	0.00	0.67	

1 - Hits were counted when correct and if 300ms < t < 2000 ms. 2 - Best achievable result in this experiment were 60 hits. 3 - Hits were counted when correct and if 1000 ms < t < 2000 ms. 4 - Best achievable result in this experimental condition were 12 correct hits. 5 - Under the sound task, there were many late responses, i.e. t > 2000 ms.. However, these late responses could be observed for all participants and no significant difference between groups could be shown. (*) - trend-level significance.

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Suppl. Table 3. Analysis of head movement with regard to group and experimental condition - second experimental setup -

	ASD	SD	TD	SD	t value	p value	Cohen‘s d
session 1							
x-translation	0.63	0.70	0.37	0.28	0.99	0.05*	
y-translation	0.48	0.16	0.37	0.32	0.89	0.39	
z-translation	1.08	0.46	1.21	0.47	-0.59	0.98	
x-rotation	0.02	0.01	0.02	0.01	-0.60	0.82	
y-rotation	0.01	0.01	0.01	0.00	1.16	0.03*	
z-rotation	0.01	0.01	0.01	0.01	0.78	0.07(*)	
session 2							
x-translation	0.67	0.86	0.31	0.18	1.17	0.01*	
y-translation	0.39	0.21	0.24	0.12	1.82	0.22	
z-translation	0.95	0.66	0.70	0.46	0.88	0.23	
x-rotation	0.01	0.01	0.01	0.01	-0.32	0.71	
y-rotation	0.01	0.01	0.01	0.00	1.70	0.06(*)	
z-rotation	0.01	0.02	0.01	0.00	1.01	0.02*	

*Translational head movement reported in mm, rotational head movement in degree. n = 16. * significant difference between groups. (*) trend level significant difference between groups.*

9. Erklärung zum Eigenanteil

Die vorliegende Doktorarbeit entstand im Rahmen einer Studie zur Verarbeitung emotionaler Signale bei Autisten, die von der Arbeitsgruppe Affektive Neuropsychiatrie unter Leitung von Herrn Prof. Dr. med. Dirk Wildgruber an der Universitätsklinik für Psychiatrie und Psychotherapie koordiniert wurde.

Mein Beitrag bestand in der Rekrutierung der Probanden, der Durchführung von MRT-Untersuchungen, Verhaltensexperimenten und der Interviews, der Auswertung der Fragebögen und MRT-Daten, der Interpretation der Daten, sowie schließlich der Diskussion und Einordnung der Ergebnisse in den Kontext der aktuellen wissenschaftlichen Literatur. Darüber hinaus präsentierte ich einen Zwischenstand der Analysen als Kongressbeitrag in Form eines Posters auf der Jahrestagung der Organization for Human Brain Mapping 2014 in Hamburg. Ein Teil der Daten wurde von mir als Originalarbeit im Journal for Neural Transmission veröffentlicht - als Erstautor schrieb ich das Manuskript und erstellte die Graphiken und Tabellen[21].

Im Vorfeld meiner Arbeit waren das Konzept für die Studie und das Studiendesign bereits von Frau Dr. rer. nat. Carolin Brück, Herrn Dr. med. Benjamin Kreifelts, Herrn Prof. Dr. med. Dirk Wildgruber und Herrn Prof. Dr. med. Thomas Ethofer entworfen worden. Die verwendeten Stimuli des AV Integrationsexperiment und des Experimentes zur Gelächterverarbeitung stammen von Herrn Dr. Kreifelts, Herrn Prof. Wildgruber und der Arbeitsgruppe.

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[21] Der Publikation wurde folgende Eigenanteilserklärung vorangestellt:
„E. Hoffmann and C. Brück contributed equally to the work. E. Hoffmann recorded fMRI and behavioral data, performed data analysis and assessment of the results, designed graphics and tables, and wrote the manuscript. C. Brück designed the study, wrote the ethic statement, recorded fMRI and behavioral data, gave advice regarding the data analysis and revised the manuscript. B. Kreifelts helped with the study design, provided the stimulus material for the AV integration experiment, recorded fMRI data, advised the programming of analysis scripts and gave valuable input for the manuscript. T. Ethofer recorded fMRI data and gave advice on the manuscript. D. Wildgruber was senior author of the study, which he co-designed. He also assessed and discussed results, and gave advice on the manuscript.“
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Frau Dr. Brück schrieb den Ethikantrag. Die MRT-Messungen führten Frau Dr. Brück und ich zusammen mit den Ärzten Herrn Dr. Kreifelts, Herrn Prof. Dr. Thomas Ethofer und Herrn Dr. med. Jonathan Wolf durch. Die behavioralen Daten (Fragebögen, Testungen) wurde von mir erhoben, wobei freundlicherweise Frau Dr. Brück einzelne Testungen in Vertretung übernahm.

10. Publikation

Teile der vorliegenden Dissertationsschrift wurden bereits in den folgenden Publikationen veröffentlicht:

- Hoffmann, E. (2014). Social Brain Network and Autism Spectrum Disorder: Reduced Connectivity to the Frontal Cortex. Poster presented at the 20th Annual Meeting of the Organization for Human Brain Mapping, Hamburg, Germany.
- Hoffmann, E., Bruck, C., Kreifelts, B., Ethofer, T., & Wildgruber, D. (2016). Reduced functional connectivity to the frontal cortex during processing of social cues in autism spectrum disorder. J Neural Transm (Vienna), 123(8), 937-947.

Übernommene Textpassagen sowie Abbildungen und Tabellen wurden mit Anführungszeichen gekennzeichnet, unterstrichen und mit einem Verweis auf die Publikation versehen. Die Übernahme erfolgt mit Zustimmung der Koautoren sowie des Springer-Verlages.

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