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PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - REVIEW ARTICLE

Elucidating the neurophysiological underpinnings of autism spectrum disorder: new developments

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Abstract The study of neurophysiological approaches together with rare and common risk factors for Autism Spectrum Disorder (ASD) allows elucidating the specific underlying neurobiology of ASD. Whereas most neurophysiologically based research in ASD to date has focussed on case–control differences based on the DSM- or ICD-based categorical ASD diagnosis, more recent studies have aimed at studying genetically and/or neurophysiologically defined homogeneous ASD subgroups for specific neuronal biomarkers. This review addresses the neurophysiological investigation of ASD by evoked and event-related potentials, by EEG/MEG connectivity measures such as coherence, and transcranial magnetic stimulation. As an example of classical neurophysiological studies in ASD, we report event-related potential studies which have illustrated which brain areas and processing stages are affected in the visual perception of socially relevant stimuli. However, a paradigm shift has taken place in recent years focussing on how these findings can be tracked down to basic neuronal functions such as deficits in cortico-cortical connectivity and the interaction between brain areas. Disconnectivity, for example, can again be related to genetically induced shifts in the excitation/inhibition balance. Genetic causes of ASD may be grouped by their effects on the brain's system level to identify ASD subgroups which respond differentially to therapeutic interventions.

Keywords Autism · Visual event-related potential · Mirror neuron · Connectivity · Transcranial magnetic stimulation · Excitation · Inhibition

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder which is characterised by difficulties in reciprocal social communication and interaction, as well as stereotyped and repetitive behaviours and interests. The disorder is genetically influenced with a heritability of ~80 % (Lichtenstein et al. 2010). ASD is a complex, heterogeneous disorder, with monogenetic disorders, rare single nucleotide (SNVs) and copy number variants (CNV) as well as common variation underlying the disorder. Replicated genetic risk variants are related to early brain development, by influencing synaptogenesis, neurotransmission, micro- and macroanatomic structure and function (Freitag et al. 2010; Berg and Geschwind 2012; Abrahams and Geschwind 2010). An innovative approach to study the biological role of genetic risk factors on ASD development are imaging genetic studies (Ameis and Szatmari 2012). For example, variants in neurexin-1 (*NRXN1*) and contactin-associated protein-like 2 (*CNTNAP2*) were associated with specific brain anatomy in ASD, and oxytocin receptor genetic variation influenced limbic structure and function in healthy individuals (Tost et al. 2010; Meyer-Lindenberg et al. 2011). To better understand common, but also specific, genetic risk factor related, underpinnings of ASD, the combination of genetic and brain imaging data will provide insights in the pathophysiology of ASD, and ultimately will help to identify targets for a causal therapy. The development of biomarkers for ASD as well as for genetically defined, more homogeneous ASD subtypes is crucial for

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future research. As there does not seem to be one unique basic mechanism that accounts for all ASD-related behaviour, neurophysiological investigation in ASD can help to disentangle the pathophysiological heterogeneity of ASD. Identifying which neural systems are affected by specific genetic risk factors will—in the long run—allow a better diagnostic classification of the respective brain dysfunction, and a differential treatment indication for subjects with ASD.

Electrophysiology represents an excellent means for this imaging genetics approach: It is easy to use even with highly impaired or very young subjects to examine developmental trajectories (Marshall et al. 2002; Boersma et al. 2011). Electrophysiology can be applied to large samples as it is widely available. Furthermore, it provides a time resolution in the millisecond range, which allows a sophisticated analysis of connectivity and other functional markers.

This review addresses the neurophysiological investigation of ASD by evoked and event-related potentials, EEG/MEG connectivity measures such as coherence, and transcranial magnetic stimulation (TMS).

The first neurophysiological studies in ASD have added to the notion that especially social brain-related neural processing abnormalities underlie ASD-specific behaviour problems. Limitations, especially of ERP studies, are that they only indicate specific brain areas which are involved in ASD pathology. In addition, specific neurocognitive models are usually tested. More recently, a paradigm shift towards testing 'mechanistic hypotheses' about basic neural network activity has evolved, which aims at explaining the complex cognitive and behavioural ASD phenotype by basic and global neural brain function such as changes in connectivity or excitability.

To illustrate the mechanisms and the pathophysiological heterogeneity underlying ASD-specific social interaction deficits, we have chosen to present research on the mirror neuron system and on visual perception as two paradigmatic examples of neurophysiological findings in ASD. A systematic review of all neurophysiological findings would be beyond the scope of this review.

The mirror neuron hypothesis of ASD has tried to relate deficits in the mirror neuron system to ASD-typical behaviour deficits such as in imitation, theory of mind, and empathy (Williams et al. 2001; Dapretto et al. 2006). The mirror neuron hypothesis assumes that specific brain areas (e.g. the motor system) are involved in social perception, and that mirror neuron dysfunction might therefore explain ASD-specific social interaction problems. In this article, we will discuss a line of research that has mainly focussed on EEG coherence measures associated with motor imitation. We show that the results differ largely between the studies depending on the examined samples, and discuss possible explanations for these findings.

To give an example of classical ASD research which identified neural correlates of behavioural symptoms, we review visual event-related potential (ERP) findings on facial emotion recognition. Recent results show that not only highly specialised areas of the social brain are underactivated in ASD (as reflected by deficits in the so-called N170 component) but that perception deficits can be tracked down to early *basic visual processing*, especially in ERP components which are produced by magnocellular visual pathways such as P100 (Rudvin et al. 2000). In line with these findings, recent research suggests that ASD-specific brain function may rather be characterised by reduced connectivity within the entire visual system (Kleinhans et al. 2008a, b) than by a circumscribed dysfunction of a highly specialised single brain area or network. Therefore, in an approach to relate ASD symptoms to more basic neural function, *cortico-cortical disconnectivity* has been postulated to underlie the replicated visual social perception deficits and other ASD symptoms. Cortico-cortical disconnectivity can result from neuronal *excitation/inhibition imbalance* (Wilson et al. 2007) which also seems to be related to specific genetic risk factors of ASD, e.g. variants in glutamatergic genes or the Fragile X syndrome (Belmonte and Bourgeron 2006). Fragile X syndrome is one of the major genetic risk factors for ASD (Hatton et al. 2006), and comes along with reduced connectivity in large-scale cortical networks (Hall et al. 2013).

Mirror neuron system deficits in ASD—heterogenous findings

A theory on the neural basis of ASD that has greatly gained in popularity over the past few years is the so-called broken-mirror hypothesis of autism (Williams et al. 2001; Dapretto et al. 2006). This theory postulates that a substantial amount of ASD symptoms is caused by deficits in the functionality of the so-called mirror neuron system (MNS). Mirror neurons are neurons that are active both during the observation and execution of object or goal directed actions (Rizzolatti and Craighero 2004). They were first discovered in the cortex of monkeys; but due to evidence from functional imaging studies, it is assumed that a mirror neuron network consisting of the inferior frontal gyrus (IFG), the adjacent ventral premotor cortex (vPMC) and the inferior parietal lobule (IPL) also exists in the human cortex (see Iacoboni and Dapretto 2006 for an overview).

There is considerable overlap between behavioural and cognitive deficits typical for ASD and the postulated functional properties of the MNS. The MNS is considered to be crucial for imitation and thereby social learning (Iacoboni 2005), as well as the decoding of the intention

behind an action (Iacoboni et al. 2005; Rizzolatti and Sinigaglia 2010). In addition, the MNS may also directly be involved in cognitive processes such as language (Rizzolatti and Arbib 1998; Ramachandran 2000), theory of mind (Gallese and Goldman 1998), or cognitive empathy (Carr et al. 2003).

A parameter that allows us to study mirror neuron activity during the performance of different behavioural or cognitive tasks using electroencephalography is so-called μ-suppression (or μ-desynchronisation). The μ-rhythm is an oscillation between 8 and 13 Hz generated by the sensorimotor cortex, recorded at electrodes C3, C4 and Cz. A decrease in μ-activity reflects stronger desynchronisation of the activity in underlying neuron populations and is associated with activation of that area (Pfurtscheller et al. 1997). Corresponding to the properties of the MNS μ-suppression occurs when goal or object directed actions are either observed or executed (Muthukumaraswamy et al. 2004).

Several studies have used EEG and μ-suppression to investigate possible MNS dysfunction in ASD. Most experiments used similar methodology, e.g. comparison of μ-suppression in response to observation and execution of hand movements and various control conditions, but did not yield consistent results (Table 1).[1]

Looking at ASD and control participants of a wide age range, one study found that control participants showed μ-suppression both, while watching and executing hand movements, whereas individuals with ASD only did when they were performing the hand actions themselves (Oberman et al. 2005). Another study that yielded similar results also found that μ-suppression during action observation correlated with imitation abilities in adults with ASD (Bernier et al. 2007).

Furthermore, it was reported that the familiarity of the person whose action was observed (self, family member or stranger) influences the degree of μ-suppression both in controls and ASD subjects. ASD children seem to show μ-suppression only when they are watching an action performed by a familiar hand (Oberman et al. 2008). In contrast, several studies did not find any differences in μ-suppression between subjects suffering from ASD and healthy controls. Raymaekers and colleagues (2009) attempted to replicate Oberman's study from 2005 but did not find any significant group differences. Correspondingly, Fan et al. (2010) found that individuals with ASD did indeed perform worse behaviourally in a condition where they had to imitate hand movements while μ-suppression was intact.

The observed heterogeneity in results of studies with different independent samples points towards the broad variation in ASD phenotypes (Jones and Klin 2009). Following this logic, MNS dysfunction may not be a universal explanation for empathy deficits in ASD. There may be subjects with ASD with intact MNS functioning, and a smaller subgroup that shows deficits. MNS deficits might also be linked to specific behavioural characteristics and ASD symptoms. Bernier and colleagues (2013), for example, tried to relate MNS dysfunction to imitation abilities and found that the ability to imitate facial gestures and μ-suppression during the observation of hand gestures was correlated. Another study also suggested that visual attention might play a role, as intact fixation patterns were found alongside intact μ-suppression (Fan et al. 2010). The same study also found that the amount of μ-suppression was positively correlated with reported communication skills in the Autism Diagnostic Interview-Revised. It is therefore important for future research to pay close attention to the exact diagnostic characteristics of subjects with ASD and to further look into factors that might be related to MNS dysfunction. As mentioned before, ASD is a disorder with broad phenotypic heterogeneity such as a great variability in symptoms (Jones and Klin 2009) and neuropathology (Amaral et al. 2008), and it has long been suggested that no single comprehensive explanation can be found to explain the disorder (Happé et al. 2006). Assuming that the heterogeneous results of the reported studies represent the heterogeneity within the autism spectrum, and not methodological differences in study design or execution, μ-suppression could be a potential marker for an ASD subgroup with MNS deficits. Future studies therefore should focus on investigating this possibility, using μ-suppression as a neurophysiological marker to define subgroups of ASD, which would have the potential to further focus research and relate neural and behavioural phenotypes to specific genetic risk factors.

Face processing in ASD—from basic visual processing to specialised pattern recognition modules

Impairments in face processing abilities at the behavioural level are frequently reported findings in subjects with ASD (Blair et al. 2002; Boucher and Lewis 1992; Boucher et al. 1998; Tantam et al. 1989). Especially, the processing of facial expressions of emotions has often been found to be impaired (Bal et al. 2010; Ashwin et al. 2006; Corden et al. 2008; Howard et al. 2000; Wallace et al. 2008). Going beyond behavioural studies, neural correlates of impaired face processing and facial emotion recognition were

[1] This table only summarises a selection of studies regarding μ-suppression in ASD and is not an exhaustive account of all studies and results published to date. Note that reported sample sizes always refer to the number of participants that were actually included in data analysis.

Table 1 Neurophysiological studies on the mirror neuron system in ASD

Authors	Sample	Task	Results
Bernier et al. (2007)	14 high functioning adults with ASD mean age 23.6 ± 4.9 15 IQ- and age-matched controls mean age 26.7 ± 8.7	Resting, observe, execute, and imitate hand movement	Normal μ-rhythm attenuation during action execution but not action observation in ASD correlation between μ-desynchronisation and behavioural imitation skills
Bernier et al. (2013)	19 children with ASD mean age 6.4 ± 1.3 19 age-matched controls mean age 6.9 ± 1.5	Resting, observe, and execute hand actions	Comparable μ-suppression across groups But subgroups in each group showed both lack of μ-suppression and during action observation and poorer imitation abilities
Fan et al. (2010)	20 participants with ASD mean age 17.7 ± 4.5 20 control- participants mean age 17.5 ± 4.7	Execute and observe hand actions, observe moving dot	Both ASD and control group showed stronger μ-suppression for observing hand actions than for observing the moving dot ASD patients made more errors while imitating hand actions but showed normal μ-suppression correlation between μ-suppression in hand action observation condition and communication subscale of ADI-R
Oberman et al. (2005)	10 participants with ASD mean age mean age 16.6 ± 13.0 10 age- and gender-matched controls mean age mean age 16.5 ± 13.6	Viewing of: hand actions, bouncing ball, visual noise or executing hand actions	Control subjects showed significant μ-suppression both during observation and execution of hand actions while participants with ASD only showed μ-suppression during the execution of hand-actions
Oberman et al. (2008)	13 children with ASD 13 age- and gender-matched controls mean age 10.2 ± 1.4	Viewing videos of: unfamiliar hand, familiar hand or the participant's own hand performing the same hand-action; bouncing balls	Significant main effect of familiarity controls showed μ-suppression to all hand-actions children with ASD showed sign. μ-suppression only to familiar hands performing hand movements.
Raymaekers et al. (2009)	20 children with ASD mean age 11.2 ± 0.3 19 age- and IQ-matched controls mean age 10.7 ± 0.3	Viewing of: hand actions, bouncing ball, visual noise or executing hand actions	Both groups showed μ suppression to both observed and executed hand-actions. No group differences were found

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studied. One method that can be used to elucidate this question are event-related potentials (ERPs) that have the advantage of being a direct measure of neural activity in the human cortex, while at the same time providing very high temporal resolution.

Visual ERP components

ERPs can map the processing of visual stimuli from the first cortical processing stages in primary visual cortex to later cognitive processes such as working memory updating and face identification.

One of the earliest visual components is the P100, which represents early stages in visual processing such as the perception of low spatial frequencies and a first rough sketch of the overall structure of the visual scene (Allison 1999). It is considered to be generated in striate and extrastriate areas (Whittingstall et al. 2007; Shigeto et al. 1998; Di Russo et al. 2002; Clark et al. 1994) and has been suggested to represent magnocellular processing (Rudvin et al. 2000). It has been shown that already in the P100, effects of face sensitivity are evident (Taylor 2002; Herrmann et al. 2005a).

One of the most frequently studied components in connection with face processing is the so-called N170, which is considered to be face sensitive[2] (Bentin et al. 1996, 2007; Rossion and Jacques 2008; Ganis et al. 2012; Schendan and Ganis 2013) and represents the structural processing of faces (Bentin and Deouell 2000; Eimer 2000c). Both the fusiform gyrus (Herrmann et al. 2005b) and the superior temporal sulcus (Itier and Taylor 2004) have been suggested as possible sources of the N170-component. It has been proposed that the child P400 can be seen as a precursor or homolog of the N170 because it can be observed at similar electrode sites as the N170 (Haan et al. 2002; Halit et al. 2003) and shows comparable patterns of face sensitivity (Haan and Nelson 1999), despite being of a different polarity.

Another component that needs to be mentioned is the N400 which is sensitive to facial identity and familiarity (Eimer 2000a; Bentin and Deouell 2000).

[2] The face specificity of the N170 (face specificity indicating the existence of a specialised module for face processing) is a subject that has been discussed extensively in the face processing literature. While some argue that the effects that were originally termed face-specific are mainly due to poorly controlled stimulus parameters (namely differences in "interstimulus perceptual variance" between faces and other objects (Thierry et al. 2007)), others have refuted this argument. To our understanding the N170 can at least be called face sensitive (Rossion and Jacques 2008; Bentin et al. 2007; Ganis et al. 2012; Schendan and Ganis 2013). Here, the N170 is defined as a sensitive marker for faces processing compared to other visual control stimuli. For a detailed discussion of this subject see e.g. Everett (2013).

For successful face processing, it is important that all of the above-mentioned processing steps work well individually but also that they interact efficiently. In the following paragraphs, we will first look at deficits in these processing stages in ASD and will then give a short outlook on possible problems regarding their interaction.

N170—face-sensitive processing

The N170 is one of the most frequently examined ERP components regarding face processing both in healthy subjects and in ASD. Several studies examined the N170 with regards to facial familiarity and face inversion, both indicating different aspects of expertise and efficiency in face processing.

Looking at the formation of familiarity of faces, Churches and colleagues (2012) found that the N170 was generally reduced in ASD subjects representing deficits in early visual processing of faces, while they also failed to show changes in ERP responses typical for the formation of new face representations. However, a similar study did not find any difference in early visual processing stages in ASD, while performance on a behavioural face-memory task was significantly poorer in the ASD group (Webb et al. 2010). The authors argued that certain experimental parameters such as cueing participant's attention using a cross-hair or the level of task demands might influence whether individuals with ASD show atypical processing patterns or not.

To further examine the nature of possible deficits in face processing in ASD, other studies have also used the comparison of ERPs in response to inverted and upright faces. An advantage for the processing of upright faces is thought to represent specialisation of the visual system for the processing of these stimuli. On a neurophysiological level, this effect can be observed, for example, in the form of a delayed and enhanced N170 following inverted faces (Itier and Taylor 2002; Rossion et al. 1999; Eimer 2000b).

An experiment, in which houses, upright and inverted faces were presented, showed intact N170 and P1 responses in ASD subjects for the processing of upright faces (larger amplitudes to faces compared to houses) but ASD subjects failed to show differential responses for inverted compared to upright faces (Webb et al. 2012). Several other studies did also find abnormal ERP patterns following face inversion in ASD. One study found that children with ASD did not show a face inversion effect for P100-amplitude, while the N170 was generally delayed independent of stimulus type (Hileman et al. 2011). Another study that looked at the inversion effect in adults with ASD reported longer N170-latencies for faces but not for objects and also found a lack of inversion effect in ASD adults (Dawson et al. 2002).

These findings indicate, on the one hand, that results are dependent on stimulus parameters and task demands, especially the cueing of visual attention. On the other hand, they show to some degree a lack in expertise and specialisation for the processing of upright human faces in ASD.

Facial emotion recognition

Seeing that there are already deficits in general face processing, it is interesting to investigate whether the same or even greater deficits are also evident during the processing of facial expressions of emotion.

When we look at facial emotion recognition (FER) in children with ASD, results are not very clear. For example, a study looking both at children and adults with ASD found no differences on an emotion-labelling-task when comparing children with ASD and age-matched controls, while adult subjects with ASD showed delayed P100 and N170 latencies and lower N170 amplitudes compared to control subjects of the same age (O'Connor et al. 2005). Another study did not find any ERP differences which were specific for the processing of emotional faces, but observed delayed latencies in early components for neutral and emotional faces as well as control stimuli (Apicella et al. 2013).

In addition, it was shown that ASD children had deficits in an implicit emotion-processing task regarding both P100 and N170-latency, and P100-amplitude when compared with age-matched controls, but only showed a decreased P100-amplitude when compared with verbal equivalent age-matched control children (Batty et al. 2011). This demonstrates the importance of adequate matching to disentangle delayed development, which often occurs in ASD, from processing deficits that are uniquely characteristic for ASD.

As mentioned above, attention to facial stimuli might also have a strong influence on face processing deficits reported in ASD. Therefore, another interesting question is in how far these deficits are evident across different modes of processing and if, for example, facilitation of attention or the explicit and intentional processing of faces can compensate deficits.

In an experiment where participants were instructed to perform a one-back memory task while either focussing their attention on pictures of neutral faces or on pictures of objects (chairs) presented in random order, it was found that healthy controls showed an increased N170 amplitude when their attention was on faces. Participants with Asperger's Syndrome, however, did not show this effect (Churches et al. 2010). This indicates that individuals with ASD were not able to recruit more neural processing capacity for the processing of faces even when they tried to attend to them. In another study, where the attentional focus was only shifted between different properties of the same facial stimuli (discriminating gender or discriminating emotional vs. neutral expressions), no ERP differences between controls and ASD children were found, although a dipole source analysis indicated different networks underlying face processing in ASD (Wong et al. 2008).

Although only two studies have investigated attentional effects on face processing directly (Churches et al. 2010; Wong et al. 2008), there are also studies indicating that especially the cueing of visual attention results in normal ERP responses in participants with ASD (Webb et al. 2010, 2012). This suggests that attentional top–down mechanisms might be disrupted thereby possibly reducing the time individuals with ASD spend looking at faces (or certain features of a face) which in turn might cause abnormal or less effective processing of social information from those faces.

Developmental aspects

An advantage of EEG, and thereby ERP analysis, is that it is well tolerated even by very young children suffering from ASD. Dawson and colleagues (2002) found, for example, that face processing deficits are already evident in ASD at 3–4 years of age. Children suffering from ASD did not show differential ERP responses to seeing their mothers versus seeing a stranger's face, while typically developing children (TDC) did. However, higher P400- and Nc-amplitudes could be observed in ASD children when they were looking at their favourite toy compared to an unfamiliar toy. In another study that compared age-matched groups of ASD children, TDC and children with developmental delay, children with ASD showed shorter latencies to objects than to faces and also higher amplitudes to objects in the precursor N170 component compared to the other groups (Webb et al. 2006). These results show that already at 3–4 years of age, deficits in face processing are evident in children with ASD while they show intact or facilitated processing of objects. A more recent study that looked at the processing of familiar and unfamiliar faces in 18–47 months old children with ASD, suggests that the deficits observed in ASD in early childhood reflect delayed development of face processing abilities, which are also correlated with the level of development of adaptive social behaviour (Webb et al. 2011).

Looking specifically at FER in toddlers, it was found that typically developing children showed differential ERP responses for passively viewing fearful and neutral facial expressions, while ASD children did not (Dawson et al. 2004). This shows that the processing of emotional facial expressions is also impaired at this early stage of development in ASD.

Studies examining face processing in infants and toddlers with ASD show us that there are deficits present

already at this young age. Even though we cannot yet tell how exactly developmental changes affect these abilities in ASD, the heterogeneous findings, specifically regarding children and adolescents, suggest that it would be worthwhile investigating this aspect further. Using ERPs would seem promising in providing a better understanding of this developmental trajectory, especially when implemented in longitudinal studies.

Summary and outlook

Taken together, face processing seems to be impaired in children with ASD from a very young age. These difficulties seem to persist during development, although some studies find fewer abnormalities in older children and adolescents. Regarding adults with ASD, findings more consistently point toward deficits in early stages of visual face processing and a lack of specialisation therein (Table 2).[3] In general, early visual processing such as the processing of elementary stimulus features (P100), as well as specialised processing stages that analyse the configuration of facial stimuli (N170) is affected.

A rather encouraging finding is that face processing abilities can be improved in patients with ASD. A computerised expertise training, for example, improved ASD participants' ability to recognise faces as well as generating a normalised ERP response towards faces (Faja et al. 2012). Another study also showed that early behavioural intervention could improve children's social behaviour as well as their neural response to social stimuli (Dawson et al. 2012). These findings suggest that training and behavioural intervention can be effective tools, helping patients to gain normal skills in face processing. Future research should concentrate on optimising these interventions and making them easily available and applicable for affected patients. We hope that a refined understanding of the neurophysiological underpinnings of the respective target symptoms will help to monitor and optimise the treatment approaches.

Taking a closer look at the deficits in face processing and FER in ASD, it seems that they are not entirely explained by a lack of functioning in individual components alone, but may also be related to poor integration and interaction between different processing stages. Latency delays in visual ERP components, which are frequently reported in ASD subjects (Hileman et al. 2011; Dawson et al. 2004; Batty et al. 2011; O'Connor et al. 2005), indicate potential problems regarding connectivity within the visual system. Although these findings may suggest a slower processing speed regarding those specific processing steps alone, a more likely explanation is that deficits are not exclusively local but affect the whole face processing network and might be caused by insufficient connectivity between the areas involved.

This also indicates that disruption in early processing stages might also affect later processing stages thereby impeding these processes. A link between deficits in early visual (P1) and later, more specialised stages of the processing of social stimuli, has already been reported for the processing of human motion in ASD (Kröger et al. 2013). Correlations were found between general deficits in early stages of motion processing and abnormalities in processing stages that occurred later on and were specific to the processing of human motion.

A theoretical explanation is provided by the concept of "weak central coherence", which suggests that individuals with ASD have a visual processing style that focusses on local details of stimuli instead of focussing on the global stimulus pattern (Happé and Frith 2006). This idea ties in with eye-tracking studies that find abnormal visual scan patterns in ASD (for a short review, see Harms et al. 2010). A likely neural underpinning of this processing style is the lack of connectivity, which in turn leads to impaired top–down modulation (Happé and Frith 2006). This idea has been discussed in several theories that attribute underconnectivity either to reduced "temporal binding" of neural activity (Brock et al. 2002), lack of anatomical connections (Just et al. 2004) or weak top–down modulation (Frith 2004). Therefore, the theory of underconnectivity is a promising unifying theory trying to explain the underlying neural mechanisms of ASD.

Overarching neurophysiological concepts: functional connectivity

EEG and MEG coherence as a measure of functional connectivity

Neural oscillations play an important role in the functional interaction of spatially distant neurons (Gray et al. 1989; Buzsáki and Draguhn 2004). Due to their high temporal resolution in the millisecond range, EEG and MEG allow for examining electrical cortical oscillations across a broad range of frequencies that are not detectable with fMRI. The study of the interaction of oscillations in separate brain regions provides insight into functional connectivity of distant brain regions. In EEG and MEG studies, connectivity is commonly inferred from measures of coherence across brain regions. Coherence estimates the consistency of relative amplitude and phase between two EEG signals

[3] This table only summarises a selection of studies regarding face processing in ASD and is not an exhaustive account of all studies and results published to date. Note that reported sample sizes always refer to the number of participants that were actually included in data analysis.

Table 2 Event-related potential studies of face processing in ASD

Authors	Sample	Task	Results
Face processing in toddlers			
Dawson et al. (2002)	34 children with ASD mean age: 44.2 mos. ± 4.2 19 children with developmental delay mean age: 45.4 mos. ± 6.2 16 controls mean age: 44.8 mos. ± 4.9	Viewing of: familiar vs. unfamiliar face and favourite vs. unfamiliar toy	ASD children showed no ERP- differences for familiar vs. unfamiliar face but P400- and Nc- differences for favourite vs. unfamiliar toy
Dawson et al. (2004)	29 children with ASD mean age: 44.8 mos. ± 10 22 age-matched controls mean age: 43.7 mos. ± 7	Viewing of: neutral and fearful faces	In controls higher N300- und "negative slow wave"-amplitude for fearful compared to neutral faces no differences in ASD children
Webb et al. (2006)	27 children with ASD mean age: 45.2 mos. ± 4 18 children with developmental delay mean age: 44.8 mos ± 5 18 controls mean age: 44.4 mos. ± 7	Viewing of: familiar vs. unfamiliar face and favourite vs. unfamiliar toy	Children with ASD showed shorter latencies to objects than to faces and showed a higher amplitude to objects compared to controls and children with developmental delay
Webb et al. (2011)	16 children with ASD-18to30 mos 17 controls-18 to 30 mos. 15 controls-12 to 17 mos.	Viewing of: familiar vs. unfamiliar face	Atypical ERP responses to facial familiarity in 18- to 30-month-old toddlers with ASD compared to chronological age-matched controls, but similar ERP responses compared to younger controls with similar social behaviour
Face processing in children and adults			
Hileman et al. (2011)	27 children with ASD mean age 13.3 ± 2.8 22 age and IQ-matched controls mean age 14.4 ± 2.1	Viewing of: faces, inverted faces, vehicles, inverted vehicles	Inversion effect for P1-amplitude in controls but not ASD children slower N170-latency for both faces and cars in children with ASD
Dawson et al. (2004)	9 patients with ASD mean age 21.2 ± 8.3 12 age and IQ-matched controls mean age: 24.6 ± 6.3	Viewing of: faces, inverted faces, furniture, inverted furniture Task: count number of target stimuli (butterflies)	Slower N170 latency to faces but not furniture in ASD patients no inversion effect to faces in patients with ASD
Churches et al. (2012)	11 patients with ASD mean age 31.8 ± 6.9 11 age and IQ-matched controls mean age 30.1 ± 4.9	Viewing of unfamiliar and newly familiar faces Task: discriminating between unfamiliar and newly familiar	Larger N170 in controls compared to ASD group independent of familiarity or hemisphere ASD group showed reduced N250 for newly familiar face compared to control group
Webb et al. (2010)	29 patients with ASD mean age 22.4 ± 6.1 28 age and IQ-matched controls mean age 24.0 ± 7.0	Viewing of familiar face, repeating unfamiliar face, non-repeating unfamiliar faces and houses (targets)	No significant ERP differences between ASD and control groups But poorer performance on a behavioural face recognition task in ASD
Webb et al. (2012)	32 patients with ASD mean age 23.1 ± 6.9 32 age and IQ-matched controls mean age 23.7 ± 6.7	Viewing of upright faces, Inverted faces, houses, inverted houses, scrambled faces (targets)	No significant ERP differences between ASD and control groups to upright faces and houses, but the ASD group did not show differential ERP responses to inverted faces compared to upright faces

Table 2 continued

Authors	Sample	Task	Results
Processing of facial expressions of emotion			
Apicella et al. (2013)	10 children with ASD mean age: 10.2 ± years 15 age-matched controls mean age controls: 9.7 ± years	Implicit emotion processing task: viewing of happy fearful and neutral faces and trees Button press when target (cartoon) was shown	No ERP differences between ASD and control groups in P1 or N170
Batty et al. (2011)	15 children with ASD mean age: 10.5 ± 3.3 years 15 age-matched controls mean age: 10.5 ± 3.2 years 15 controls verbal equivalent age-matched mean age controls: 7.7 ± 3.8 years	Implicit emotion processing task: viewing of emotional faces Button press when target (non-face object) was shown	Slower P1- und N170–latency and lower P1-amplitude in ASD children compared to controls comparison with verbal equivalent age-matched controls only showed lower P1-amplitude in ASD
O'Connor et al. (2005)	Children: 15 children with ASD mean age: 11.6 ± 1.9 years, 15 age-matched controls mean age: 11.2 ± 1.8 years Adults: adults with ASD mean age: 24.6 ± 8.8 years mean, 15 age-matched controls age: 24.8 ± 8.7 years	Viewing of emotional facial expressions (happy, sad, angry, scared, and neutral) Task: label emotions verbally	Adults with ASD show slower P1 und N170-latency, as well as lower N170-amplitude (compared to control-adults) No differences between children with and without ASD
Churches et al. (2010)	15 adults with Asperger's-Syndrome mean age: 31.4 years ± 6.7 15 age and IQ-matched controls mean age: 29.3 years ± 4.6	Viewing of: furniture and neutral faces Implicit: 1-Back-Task for furniture Explicit: 1-Back-Task for faces	Higher N170-amplitude in explicit condition in controls no differences between conditions in ASD patients
Wong et al. (2008)	10 children with ASD mean age: 8.5 ± 1.5 years 12 age and IQ-matched controls mean age: 8.5 ± 1.4 years	Viewing of: happy, angry, fearful und neutral faces Task: Implicit: discriminate gender Explicit: discriminate emotional from neutral faces	No ERP differences between controls and ASD children Source analysis suggests different sources of activity for ASD children

in a given frequency band and thus provides information about the functional interaction between neural systems (Bendat and Piersol 2000; Srinivasan et al. 2007).

Functional connectivity in visual perception

Functional connectivity measured during the performance of specific cognitive tasks can provide information about the interaction of brain regions activated by the respective cognitive processes. Given the findings in visual processing and specifically face processing reported above, researchers have investigated brain connectivity during visual perception tasks in ASD.

An EEG study in adults with ASD ($n = 15$) found reduced interhemispheric coherence during visual processing of faces and inanimate objects in frequencies below 13 Hz (Catarino et al. 2013). Using MEG, reduced coherence between the fusiform face area and several other distant brain regions was demonstrated during the processing of emotional faces ($n = 17$) (Khan et al. 2013). The findings suggest that connectivity between functionally relevant brain areas may be disturbed in ASD in complex processes like facial perception. Underconnectivity may therefore be the underlying pathology leading to altered activation in the processing of social visual stimuli, namely delayed latencies reported in ERP studies (Hileman et al. 2011; Dawson et al. 2004; Batty et al. 2011; O'Connor et al. 2005). Interestingly, reduced interhemispheric connectivity between early visual areas in children with ASD ($n = 6$) was previously also reported in a simple visual perception task using flashlights (Isler et al. 2010). This suggests that connectivity deficits play a role already at early stages of basic visual perception and not only during the processing of complex social visual stimuli. While these results support an underconnectivity hypothesis, there have also been reports contradicting general underconnectivity in ASD. For example, during a picture naming task in areas relevant to visual and language processing ($n = 12$), Buard et al. (2013) found increased connectivity in MEG. This over-connectivity may be a correlate of compensation mechanisms resulting from connectivity deficits in other networks.

The specific pattern of connectivity alterations likely depends on the cognitive processes that were studied and the specific neural system involved. It also seems likely that differing connectivity patterns will be present in specific subgroups or endophenotypes of ASD. Understanding of altered connectivity may therefore provide insight into the neural basis of inter-individual variability of symptoms in subjects with ASD.

Functional connectivity during resting state

Functional connectivity in ASD has not only been investigated during the performance of cognitive tasks but also at resting state. An EEG investigation in adults with ASD ($n = 18$) found reduced long-range alpha band coherence between frontal leads and other scalp regions. At the same time, increased short-range coherence in ASD was observed at primarily temporal electrodes in the theta band (Murias et al. 2007). Another study conducted with adult ASD subjects ($n = 10$) found decreased long-range coherence in the delta band mostly in fronto-occipital connections while again local connectivity was increased. In addition, altered connectivity correlated with ASD symptom severity suggests functional relevance for ASD core symptoms (Barttfeld et al. 2011). In children with ASD ($n = 20$), reduced coherence was found primarily in the theta and delta band in both short-range and long-range connections (Coben et al. 2008). Altered resting state connectivity across various brain regions has also been demonstrated using MEG in adolescents and young adults with ASD ($n = 8$) with connectivity patterns discriminating between groups with 93.75 % accuracy (Tsiaras et al. 2011). Interestingly, aberrant connectivity in MEG in children with ASD is already observable at the age of 3–7 years ($n = 70$) (Kikuchi et al. 2013) suggesting that disconnectivity is present already during early development.

The largest study investigating EEG coherence with a very large sample of 463 ASD subjects and 571 control subjects was performed with children and adolescents with ASD. In resting state EEG, a complex pattern of reduced short-range coherence and partially reduced and partially increased long-range coherence were observed. Using coherence patterns as diagnostic markers in random split half replications resulted in a classification success of 88.5 % for the control group and 86.0 % for ASD (Duffy and Als 2012). While most studies found reduced long-range connectivity in ASD compared to controls, there have also been reports that found no group differences (Mathewson et al. 2012).

In summary, there is a series of EEG and MEG studies reporting reduced long-range connectivity in ASD at resting state. There are varying results across studies regarding the question whether short-range coherence is reduced (Coben et al. 2008; Duffy and Als 2012) or increased (Murias et al. 2007; Barttfeld et al. 2011). Conflicting results may be due to varying methods used, but may also result from the neurobiological heterogeneity of ASD. The reported investigations provide evidence for basic long-range connectivity deficits at resting state, which may represent pathological processes underlying altered functional connectivity that can be found during the execution of cognitive processes. Disconnectivity may in turn be the basis of ERP findings in ASD in specific brain areas (e. g. Hileman et al. 2011; Dawson et al. 2004; Batty et al. 2011; O'Connor et al. 2005) such as longer ERP latencies during

facial perception. As there is evidence for reduced long-range connectivity in ASD from early childhood up to adulthood, disconnectivity appears to be a pervasive alteration of neural functioning in ASD. However, longitudinal studies tracking neural connectivity in ASD across development would be necessary to understand the maturational trajectories of disconnectivity.

The results of Duffy and Als (2012) support the idea that EEG coherence can be used as a diagnostic marker for ASD, although replications in independent ASD samples will be necessary before final conclusions can be drawn. A follow-up study of the same group showed that subjects with Asperger syndrome differ regarding their connectivity patterns from other ASD subjects (Duffy et al. 2013) again supporting the notion of distinct pathological processes in different subgroups. Therefore, disconnectivity patterns may in the future provide insight into the heterogeneity of ASD and help in the development of individualised biomarkers for specific ASD subtypes.

Genetically influenced alterations of excitation and inhibition may be the basis of altered connectivity

Genetic basis of an altered excitation/inhibition balance

It has been hypothesised that an altered excitation/inhibition balance may cause at least some forms of ASD (Rubenstein and Merzenich 2003). ASD is a highly heritable but genetically heterogeneous disorder (Freitag 2007). Molecular genetic findings in idiopathic ASD suggest that genes relevant to excitatory and inhibitory neurotransmitter systems are involved in the pathogenesis of ASD (Freitag et al. 2010) and may thus form the basis of an excitation/inhibition imbalance. In addition, monogenetic disorders like, e. g. Fragile X syndrome (FRAX) provide a pathogenetic model suggesting an altered excitation/inhibition balance. FRAX has a high prevalence of ASD-like symptoms and is associated with altered glutamatergic and GABAergic neurotransmission (Hagerman et al. 2010). Further evidence for a role of excitation/inhibition imbalance comes from animal models as mutations leading to an alteration of excitatory and inhibitory neurotransmission result in ASD-like phenotypes in mice (Tabuchi et al. 2007; Jedlicka et al. 2013).

An excitation/inhibition imbalance may cause alterations of functional connectivity in ASD by influencing cortical oscillations (Wilson et al. 2007). Therefore, studies investigating altered inhibition and excitation may provide a link between molecular findings implicating excitatory and inhibitory neurotransmitters and neurophysiological findings of connectivity deficits in ASD.

Studies of cortical excitation and inhibition with transcranial magnetic stimulation (TMS)

There are limited possibilities to study the balance of excitation and inhibition in vivo in humans. Transcranial magnetic stimulation (TMS) is a neuroscientific technique that enables examining intracortical excitation and inhibition. TMS makes it possible to activate small areas of the cerebral cortex in humans by inducing a brief magnetic field with an electromagnetic coil. The use of specific stimulation protocols (Kujirai et al. 1993) and the combination of TMS with other neuroscience methods such as EEG and MRI (review in Ziemann 2011) make TMS a versatile tool for neuropsychiatric research.

Paired pulse TMS (ppTMS) (Kujirai et al. 1993) makes it possible to probe the balance of intracortical inhibition and intracortical facilitation by applying two successive TMS pulses. The motor response (MEP) produced by the second pulse (the actual test pulse) can be inhibited or facilitated by a preceding subthreshold pulse (conditioning pulse) depending on the time interval separating the two pulses. This approach has been successfully applied to study cortical mechanisms in neuropsychiatric disorders in children like ADHD and tic disorders (Moll et al. 1999; Gilbert et al. 2011).

The first study to investigate inhibition and facilitation with ppTMS in a relatively small sample of ASD subjects ($n = 10$) found no significant group differences (Theoret et al. 2005). An even smaller study including five subjects with Asperger syndrome found paradox effects (i.e. facilitation in inhibition paradigms) in two ASD participants on single subject level but reported no systematic group effects for ASD (Oberman et al. 2010). Apart from the lack of power due to the small sample sizes, the very broad age range and the diagnostic heterogeneity of the ASD samples may have contributed to the contradictory results in these studies. In a larger ppTMS study using standard protocols including 25 ASD individuals (high functioning autism (HFA) and Asperger syndrome), reduced short intracortical inhibition (SICI) was found in subjects with HFA but not in subjects with Asperger syndrome (Enticott et al. 2010). This preliminary study was followed by a larger sample of 36 adolescents and adults with ASD using the same approach. Again, SICI was found to be reduced in a subgroup of ASD patients with early language delay but not in ASD in general (Enticott et al. 2013).

In summary, results of TMS studies do not support a general alteration of the equilibrium of inhibition and excitation in ASD, but point towards a role of altered intracortical inhibitory processes in a specific subgroup of ASD individuals with infantile autism and language delay but not with Asperger syndrome. As SICI is mediated through GABA-A receptors (Ziemann 2003), these TMS

studies may provide a link between molecular findings implicating the GABAergic system in ASD (e. g. Collins et al. 2006; Fatemi et al. 2008) and neurophysiological functions. Future studies combining genetics with TMS may bridge molecular genetic findings with neurophysiological processes in ASD and may thus help identifying biologically founded endophenotypes.

Interestingly, SICI deficits in ASD subjects with language delay were only found in the left hemisphere (Enticott et al. 2013) in which systems associated with language processing are typically located. The asymmetry of SICI deficits is conclusive with several resting state EEG studies showing an atypical asymmetry of EEG power across different frequency bands (Cantor et al. 1986; Stroganova et al. 2007; Burnette et al. 2011) which may be related to atypical hemispheric lateralization of cortical functions in ASD. The left-sided reduction of SICI in ASD with language delay is also in line with fMRI results showing abnormal functional lateralization of language in ASD (Kleinhans et al. 2008a, b) and points towards a possible role of cortical inhibitory processes in the maintenance of cerebral asymmetry.

The TMS investigations conducted so far show no evidence for an alteration of intracortical facilitation or basic excitability parameters as MEP values and TMS motor thresholds (Theoret et al. 2005; Enticott et al. 2010, 2013; Oberman et al. 2010). Therefore, there is currently no evidence for abnormalities in excitatory neurotransmission from TMS.

As no TMS investigations in children have been published so far, it is unclear whether the reported results, particularly the results regarding impaired SICI, can be generalised to children and what the developmental trajectories of altered cortical functions may be. Also, studies should address the question of regional specificity of deficits, as the studies conducted so far targeted the primary motor cortex. As TMS combined with synchronous EEG (TMS–EEG) allows for examining cortical inhibition in other cortical regions (Daskalakis et al. 2008) TMS–EEG studies may provide insight into the functioning of relevant areas such as supplementary motor cortices or language areas. Also, as TMS–EEG makes it possible to study functional connectivity (Miniussi and Thut 2009), combined TMS–EEG investigations may clarify the relationship of altered excitation/inhibition balance and connectivity deficits in ASD.

Conclusion

Our aim in the current review was to give an overview of how neurophysiological methods can contribute to the understanding of ASD as a neurobiologically defined disorder. First, we discussed a classical perspective on ASD research that aimed to explain behavioural abnormalities in ASD through differences in neural processing patterns. Research in the area of face processing has been able to show that patients with ASD often show slower and less specialised visual processing of faces. Looking at another domain of social processing, we identified very heterogeneous results, with presumably only a subgroup of ASD individuals showing deficits in the mirror neuron system.

We also showed that these deficits can be broken down into more basic neural mechanisms such as disconnectivity which can in turn be related to genetic abnormalities. We have tried to demonstrate that the interest in brain functions underlying ASD has shifted from attempts to explain ASD by pathology in a given brain region to more mechanistic approaches like the study of basic deficits in connectivity between separate brain regions and an excitation/inhibition imbalance. We argue that connectivity deficits and excitation/inhibition imbalances may be more fruitful models for explaining a range of neurophysiological findings in ASD across various brain regions. We illustrated examples of how ERP findings of deficits in specific brain regions during cognitive tasks like visual perception of social stimuli can be traced down to deficits in basic visual perception that may in turn be a result of altered connectivity. There is evidence that reduced cortical connectivity is present in ASD both during these specific cognitive processes and during resting state across a wide range of brain regions and in different frequency spectra. Furthermore, connectivity deficits seem to be pervasive throughout development. As connectivity deficits reflect alterations of the interaction of brain regions, the abnormal activation of one brain region during the processing of social stimuli may be a result of the disturbed interplay between neural systems resulting from basic connectivity deficits. Thus, functional disconnectivity may represent an example of a central pathological process in ASD.

As connectivity deficits may be based on an altered excitation/inhibition balance the study of cortical excitation and inhibition using TMS may elucidate cortical processes underlying connectivity deficits. As TMS measures of inhibition and excitation can be linked to the functioning of neurotransmitter systems (e.g. GABA), this method provides a link between neurophysiological parameters and the molecular findings in ASD.

In this review, we have illustrated that there are heterogeneous findings regarding whether subjects with ASD show abnormalities in specific neuronal systems (e. g. mirror neuron system) or not. This heterogeneity is probably based in the genetic heterogeneity of the disorder. Therefore, it is likely that there are subgroups of ASD patients, who will respond differently to therapeutic

approaches. Neurophysiological methods will help to define more homogeneous, biologically defined subgroups of ASD, and may make it possible to use neurophysiological biomarkers for a personalised medicine approach in the future. Specific individualised therapeutic approaches could be developed, such as μ-rhythm suppression neurofeedback for subjects with ASD who show mirror neuron system deficits.

In our opinion, future research on the neurophysiological underpinnings of ASD should consider the following propositions:

Studies should move away from measuring the activation of isolated brain areas. Given their excellent temporal resolution, electrophysiological methods like EEG and MEG should be applied more widely in the studies of neural connectivity. The role of connectivity deficits during cognitive processes and at rest should be investigated.

Neurophysiological investigations should try to address the relationship between altered activation of specific brain regions and the interaction of different brain regions (e.g. by combining ERP measures and connectivity measures). As neurophysiological alterations such as connectivity deficits are likely to change during brain development, studies should also address the developmental trajectories of altered brain processes.

The integration of methods such as EEG and TMS may broaden the understanding of the relationship between functional connectivity and the excitation/inhibition equilibrium and thus help in translating molecular models of ASD to human neurophysiological research. Thus, an important point of this paper is that disconnectivity should not only be examined by structural means such as synaptic density/morphology and white matter integrity but also by functional means which include neuronal synchronisation and excitability.

Overarching aims of future neurophysiological research in ASD should be:

(1) To disentangle the pathophysiological heterogeneity behind ASD symptoms, and (2) To track down the underlying neurobiology of ASD to a limited number of basic deficits in neural networks.

Instead of looking at isolated brain areas, we need to address the functional connectivity within the systems that process socially relevant information. Therefore, we need to overcome the limitations of many studies with small sample sizes and a wide variety of tasks. Instead, the formation of research consortia seems necessary, to examine large samples of ASD which allow a subgrouping approach according to pathophysiological parameters (e.g., subjects with disconnectivity in the visual system versus subjects without visual disconnectivity).

We suggest that (despite limitations inherent in any multi-centre study with many different laboratories) EEG data could also be joined from many centres to assess connectivity patterns in ASD, such as has recently been accomplished for resting state functional magnetic resonance imaging data (Di Martino et al. 2013).

In addition, large sample sizes can be genetically characterised to examine specific groups of patients with a predetermined genotype in neurophysiological studies. Risk genes identified in genome-wide association studies should be screened for their functional effects on the brain. Imaging genetics studies have begun to emerge, but are still in their infancy especially with respect to neuronal function and connectivity, moving from structure to function.

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