



Review article

A revisit of the amygdala theory of autism: Twenty years after

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ARTICLE INFO

Keywords:

Autism spectrum disorder
 Amygdala
 Face processing
 Social attention
 Functional connectivity
 Multimodal neuroimaging
 Human single-neuron recordings

ABSTRACT

The human amygdala has long been implicated to play a key role in autism spectrum disorder (ASD). Yet it remains unclear to what extent the amygdala accounts for the social dysfunctions in ASD. Here, we review studies that investigate the relationship between amygdala function and ASD. We focus on studies that employ the same task and stimuli to directly compare people with ASD and patients with focal amygdala lesions, and we also discuss functional data associated with these studies. We show that the amygdala can only account for a limited number of deficits in ASD (primarily face perception tasks but not social attention tasks), a network view is, therefore, more appropriate. We next discuss atypical brain connectivity in ASD, factors that can explain such atypical brain connectivity, and novel tools to analyze brain connectivity. Lastly, we discuss new opportunities from multimodal neuroimaging with data fusion and human single-neuron recordings that can enable us to better understand the neural underpinnings of social dysfunctions in ASD. Together, the influential amygdala theory of autism should be extended with emerging data-driven scientific discoveries such as machine learning-based surrogate models to a broader framework that considers brain connectivity at the global scale.

1. Introduction

Toward understanding the biological origin of autism spectrum disorders (ASD), the first neurobiological study dated back to the 1960s (Rimland, 1964). In 1978, similar behaviors between people with ASD and patients with frontal lobe damage were observed (Damasio and Maurer, 1978); and in 1988, positron emission tomography (PET) was used to find indirect support for abnormal brain activity in adults with autism (Horwitz et al., 1988). In the past two decades, rapid advances in neuroimaging techniques such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), magnetoencephalography (MEG), diffusion tensor imaging (DTI), and proton magnetic resonance spectroscopy (¹H-MRS) have greatly facilitated the study of regional brain function and dysfunction in autism.

One neural structure that has long been implicated in ASD is the amygdala. The amygdala is hypothesized to underlie social dysfunctions in ASD, an influential theory coined as the “amygdala theory of autism” (Baron-Cohen et al., 2000). The idea of amygdala abnormalities in autism is supported by substantial literature showing structural abnormalities (Amaral et al., 2008; Bauman and Kemper, 1985; Ecker et al.,

2012; Schumann and Amaral, 2006; Schumann et al., 2004) and atypical activation (Gotts et al., 2012; Philip et al., 2012) in the amygdala in ASD. In particular, this hypothesis is supported by rather similar patterns of deficits seen in patients with amygdala damage, who fail to fixate on the eyes in faces (Adolphs et al., 2005), single-neuron recordings in the human amygdala showing weaker response to eyes in people with ASD (Rutishauser et al., 2013), as well as neuroimaging studies showing that amygdala-mediated orientation towards eyes seen in blood-oxygen-level-dependent (BOLD)-fMRI is dysfunctional in ASD (Kliemann et al., 2012). However, it remains unclear to what extent the amygdala can account for the behaviors in ASD. In this review, we will first discuss studies that employed the same tasks and stimuli, preferably conducted by the same researchers, to directly compare amygdala lesion patients and people with ASD. Given that the amygdala alone can only limitedly explain the social dysfunctions in ASD, a network view is, therefore, more appropriate. Lastly, we discuss emerging new opportunities to better understand the neural underpinnings of ASD. We propose to employ multimodal neuroimaging approaches with data fusion as well as more sensitive physiology approaches to study the functional neural network at the circuit level in humans.

Abbreviations: ASD, Autism Spectrum Disorder; PFC, Prefrontal Cortex.

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<https://doi.org/10.1016/j.neuropsychologia.2023.108519>

Received 9 July 2022; Received in revised form 23 January 2023; Accepted 16 February 2023

Available online 17 February 2023

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2. Amygdala and autism

In the past two decades, there has been a plethora of studies using an array of cognitive tasks to investigate the functional role of the amygdala in ASD. Here, we stress the studies where ASD data, amygdala lesion data (which can show a necessary role of the amygdala), and functional data of the amygdala (neuroimaging data from controls and electrophysiology data from neurosurgical patients) are all available using the same task. These studies enable us to directly and most comprehensively elucidate the role of the amygdala in ASD.

2.1. Face perception

Faces are among the most perceived visual stimuli. Many studies have documented abnormal face processing in people with ASD (Adolphs et al., 2001; Kliemann et al., 2010; Klin et al., 2002; Neumann et al., 2006; Pelphrey et al., 2002; Spezio et al. 2007a, 2007b), and the such deficit has both a developmental (Jones and Klin, 2013) and genetic (Constantino et al., 2017) root. On the other hand, the human amygdala plays a critical role in face processing (Adolphs, 2008). It contains neurons that not only are visually selective to faces (Kreiman et al., 2000) and facial emotions (Fried et al., 1997), but also encode many aspects of faces, such as face identities (Quiñero Quiroga et al., 2005), subjective perception of facial emotions (Wang et al., 2014a), the ambiguity of facial emotions (Wang et al., 2017), facial features (Cao et al., 2021), and social trait judgment of faces (Cao et al., 2022a). Therefore, abnormal face processing in autism has been hypothesized to arise from amygdala dysfunction (Baron-Cohen et al., 2000). Direct evidence supporting this hypothesis comes from both single-neuron recordings in the human amygdala (Rutishauser et al., 2013) as well as neuroimaging studies (Dalton et al., 2005; Kliemann et al., 2012). For example, activation in the amygdala has been reported to be correlated with the time spent fixating the eyes in ASD (Dalton et al., 2005).

By far the strongest evidence supporting the amygdala's role in ASD may come from a "bubbles" task, in which participants discriminate emotions from sparsely sampled fear or happy faces. This same task has revealed reduced attention to the eyes as well as utilization of information from the eyes in judging emotions in both amygdala lesion patients (Adolphs et al., 2005) and people with ASD (Neumann et al., 2006; Spezio et al. 2007a, 2007b). Consistent with these behavioral findings, single-neuron data recorded from two neurosurgical patients with ASD showed that compared to control patients, a population of amygdala neurons in the two patients with ASD respond significantly more to the mouth, but less to the eyes (Rutishauser et al., 2013). Therefore, this task has provided the most coherent evidence that the amygdala accounts for abnormal face processing in ASD during facial emotion judgment.

Another series of studies on facial trustworthiness have also revealed a consistent pattern of behavior between amygdala lesion patients and people with ASD. Compared to controls, amygdala lesion patients judge unfamiliar individuals to be more approachable and more trustworthy, and the impairment is most prominent for faces to which controls assign the most negative ratings (i.e., unapproachable and untrustworthy looking individuals) (Adolphs et al., 1998). Using the identical task, people with ASD show a similar pattern of abnormal social judgment of trustworthiness (Adolphs et al., 2001). The functional role of the amygdala in facial trustworthiness judgment has been supported by both neuroimaging (Cao et al., 2020; Todorov et al., 2008) and electrophysiology (Cao et al., 2022b) studies. More broadly, recent studies have shown that neurons in the human amygdala encode eye gaze on facial features (Cao et al., 2021) and collectively encode the most comprehensive social trait space to date (Cao et al., 2022a), which may have a behavioral consequence likely involved in the abnormal processing of social information in autism (Cao et al., 2022a; Yu et al., 2022).

Impaired categorization of basic facial emotions has been shown in both amygdala lesion patients (Adolphs et al., 1999) and people with ASD (Adolphs et al., 2001; Kennedy and Adolphs, 2012). However, in

recent studies using an identical emotion judgment task where participants discriminate graded emotions shown in morphs of fear-happy faces, although both people with ASD and amygdala lesion patients demonstrate abnormal emotion judgment, the abnormality is different: people with ASD demonstrate reduced specificity of emotion judgment (Wang and Adolphs, 2017a) whereas amygdala lesion patients demonstrate lowered threshold to report fear (Wang et al., 2017). Functional data from neuroimaging and single-neuron recordings further showed that the amygdala tracks the degree of emotions (i.e., the intensity of fear shown in the face) as well as categorical ambiguity of emotions (i.e., how clear the emotion is signaled), although different aspects are encoded by different parts of the amygdala and subpopulations of amygdala neurons (Wang et al., 2017). Therefore, it seems that the coding of emotion intensity has a consequence on behavior, but the coding of emotion ambiguity may be carried over from other brain regions (Sun et al. 2017, 2023). The amygdala may still influence emotional judgment, but at least not the same aspect for people with ASD and amygdala lesion patients.

2.2. Social attention

Social attention refers to preferential gazes to or detection of faces or people in the presence of other competing stimuli, either using natural scenes or an array of isolated items. Using the same visual search task with social (faces and people) and non-social (e.g., electronics, food, utensils) targets and distractors, people with ASD show significantly reduced fixations on target-congruent distractors, especially for social targets, suggesting a less efficient search strategy; but amygdala lesion patients demonstrate normal behavior (Wang et al., 2014b). Notably, single neurons in the amygdala not only signal the presence of search targets but also encode category membership of the search items (Wang et al., 2018), indicating that amygdala neurons only correlate to but do not determine the search behavior. Therefore, in this case, the amygdala does not seem to account for the abnormal behavior in ASD. Similarly, using the same free-viewing task that comprehensively analyzed visual attention, people with ASD show atypical visual attention (i.e., a stronger image center bias regardless of object distribution, reduced saliency for faces and locations indicated by social gaze, yet a general increase in pixel-level saliency at the expense of semantic-level saliency) (Wang et al., 2015a), but amygdala lesion patients show eye movement patterns that are more similar to controls (Wang, 2019).

Using complex social scenes that contain faces, although both amygdala lesion patients and people with ASD spend less time looking at the eyes, there is dissociation with task conditions: whereas amygdala lesion patients look more at the eyes when the task requires social attention, people with ASD do not (Birmingham et al., 2011). This in turn indicates two different mechanisms: amygdala lesion patients may have a failure in stimulus-driven attention to social features but people with ASD may be generally insensitive to socially relevant information and fail to modulate attention as a function of task demands. Lastly, using the same change detection task, both people with ASD (New et al., 2010) and amygdala lesion patients (Wang et al., 2015b) show intact prioritized social attention for animate categories (animals and people), even though amygdala neurons have a strong categorical selectivity for pictures of animals (Mormann et al., 2011).

2.3. Other tasks

There are other amygdala lesion studies beyond social attention and face processing that shed light on the role of the amygdala in autism. When tested in the same way, both people with ASD (Kennedy and Adolphs, 2014) and amygdala lesion patients (Kennedy et al., 2009) violate personal space. And neuroimaging data show that amygdala activation is associated with close personal proximity (Kennedy et al., 2009). Lastly, to directly test whether amygdala lesion patients meet the criteria for ASD, two amygdala lesion patients were compared with

published norms from both healthy populations using a comprehensive clinical examination, the Autism Diagnostic Observation Schedule (ADOS) (Hus and Lord, 2014; Lord et al., 1989), the Social Responsiveness Scale (SRS) (Constantino and Gruber, 2012), and several other standardized questionnaires. However, neither amygdala lesion patient shows any evidence of autism across the array of different measures (Paul et al., 2010). These findings suggest that amygdala lesions in isolation are not sufficient for producing autistic symptoms.

2.4. Possible caveats

There are several possible caveats that we would like to note when we interpret the above studies.

First, although all amygdala lesion patients discussed above suffer from the same Urbach-Wiethe disease (UWD) (Hofer, 1973), the lesion contents are different (Amaral and Adolphs, 2016). It is well-known that different amygdala subnuclei are involved in different neural circuitry and functions (Janak and Tye, 2015). The basolateral amygdala is the primary source of visual input to the amygdala and the centromedial amygdala is a primary source of output to subcortical areas relevant for the expression of innate emotional responses and associated physiological responses (LeDoux, 2007). The centromedial amygdala provides most of the amygdala projections to hypothalamic and brainstem nuclei that mediate the behavioral and visceral responses to fear (Aggleton et al., 1980; Davis, 1992; Fudge and Tucker, 2009). Furthermore, the projection neurons in the central nucleus are mostly inhibitory, and are, in turn, inhibited by inhibitory intercalated cells in the lateral and basal amygdala. Disinhibition through this pathway is thought to lead to the expression of emotional responses (LeDoux, 2007). Given the differential roles of different amygdala subnuclei, different lesion contents may lead to different behaviors. For example, in one study (Wang et al., 2017), three amygdala lesion patients with most of the basolateral complex of the amygdala lesioned but the centromedial nucleus intact showed a lowered threshold for reporting fear, whereas in another study (Adolphs et al., 1994), patient S.M. who had complete amygdala lesion including both basolateral and centromedial subnuclei (Adolphs, 2016; Buchanan et al., 2009) showed an increased threshold for reporting fear (the opposite of (Wang et al., 2017)). Consistent with (Wang et al., 2017), another group of five patients with only basolateral amygdala damage demonstrated a hyper-vigilance for fearful faces (Terburg et al. 2012, 2012v; van Honk et al., 2016b). A putative mechanism explaining such differentiation in behaviors between the two types of amygdala lesion patients is that partial amygdala lesions remove a normal inhibitory brake on fear sensitivity and result in exaggerated sensitivity to emotion mediated by the disinhibited central nucleus. This mechanism is further supported by optogenetic work in rodents that specific activation of the terminals that project from the basolateral amygdala to the central nucleus reduces fear and anxiety in rodents, whereas inhibition of the same projection increases anxiety (Tye et al., 2011). Together, different amygdala subnuclei are involved in different neural circuitry and functions and it is thus important to take amygdala lesion contents into consideration when we interpret results and compare between studies.

Relatedly, human single-neuron recordings have shown that different subsets of amygdala neurons are involved in different aspects of face processing (Cao et al., 2022b; Wang et al., 2017) and social attention (Wang et al., 2018); and the amygdala demonstrates a flexible encoding of facial trustworthiness (Cao et al., 2022b) (which is also shown by neuroimaging (Cao et al., 2020)). Therefore, detailed lesion contents, as well as task instructions, matter when we compare amygdala lesion patients with people with ASD.

Second, although amygdala lesion patients, in general, show consistent responses (see (Terburg et al., 2012; Wang et al., 2015b; Wang et al., 2017) for examples), it is also important to note that a multitude of factors can fundamentally alter the behavioral manifestations of a lesion, including the etiology and developmental time course

of the lesion, the extent of damage, the brain's compensation following the damage, and the unique personality and set of life experiences, making each lesion case-specific (Feinstein et al., 2016). On the other hand, autism spectrum disorders are well known to be highly heterogeneous at the biological and behavioral levels, and there will likely be no single cause for the diverse symptoms defining autism (Happé et al., 2006). For example, inter-subject correlations in the pattern of evoked brain activation are reduced in the ASD group and such idiosyncratic responses are in turn also internally unreliable (Byrge et al., 2015). Therefore, the heterogeneity in both amygdala lesion patients and participants with ASD may result in inconsistent task responses.

Third, both ASD and the above-mentioned amygdala lesions are developmental. Calcification of the amygdala in UWD seems to start early in childhood and possibly even at birth, although this may depend on the type of genetic mutation and slowly progresses throughout adolescence and adulthood (van Honk et al., 2016a). Human neuroimaging studies show that the typically developing amygdala continues to undergo substantial growth throughout childhood and well into adolescence (Schumann et al., 2004), and the amygdala may play a more critical role early in the developmental neurobiology of social and emotional orienting, but a less relevant role in this process in adulthood (Schumann et al., 2011). Differences in neurodevelopmental trajectories between people with ASD and amygdala lesion patients may result in discrepancies in task performance.

Fourth, amygdala lesion patients may have compensatory functions provided by other brain regions over time (e.g. (Becker et al., 2012)),. The compensated functions may account for the discrepancies in task response compared with people with ASD. It is therefore important to compare the above findings with results from patients with acute-onset amygdala lesions (e.g., caused by surgical resections) or "lesions" induced by transient electrical stimulations.

Lastly, most of the above studies were performed in high-functioning participants with ASD. It remains an open question how well these findings can be generalized to other individuals (especially the low-functioning ones) on the autism spectrum. In addition, specific to single-neuron recording studies, all participants with ASD and controls have a diagnosis of intractable epilepsy, and it is unrealistic to entirely discount the possibility that the observations are affected by epilepsy. However, several controls have been suggested. First, findings made from data recorded within the "epileptic" tissue (defined as electrode locations within the seizure onset zone (SOZ)) can be compared to the data from the "healthy" tissue (defined as outside the SOZ). This is possible because many electrodes will (retrospectively) have been located outside the SOZ. This approach has yielded new insights into the processes that are vs. are not affected by the SOZ (Lee et al., 2021). Second, behavioral data from neurosurgical patients can be compared with that from participants without epilepsy (Wang et al., 2017); and neural data can be cross-validated by other approaches (e.g., fMRI, EEG; see (Sun et al., 2023; Wang et al., 2017) for examples). Together, it is important to note the subpopulation of ASD for investigation and consider generalizability of ASD in future studies.

2.5. Summary

In summary, direct comparisons between people with ASD and amygdala lesion patients using the same tasks indicate that the amygdala can only account for some deficits in face processing but not visual attention (neither top-down nor bottom-up) in ASD. Because amygdala lesions do not cause autism (Paul et al., 2010) and the amygdala alone may only explain a limited number of deficits in ASD, a network view may be more appropriate (Stanley and Adolphs, 2013): abnormal connections between the amygdala and other brain regions may better explain the atypical function in the amygdala seen in individuals with ASD. Although there may be pathology within neurons of the amygdala itself, a single brain region is unlikely to account for a complex brain disorder such as ASD.

3. Functional connectivity and autism

Since it has not been successful to explain autism from the point of view of focal brain region abnormality due to the complexity and heterogeneity of ASD, network-level analysis of atypical functional connectivity, which characterizes the “cross-talk” between different brain areas, becomes a promising direction for studying ASD. Specifically, functional connectivity is defined as the strength to which activity between a pair of brain regions covaries or correlates over time (Friston, 1994). It is calculated as the statistical dependence between time series of electrophysiological activity and (de)oxygenated blood levels in distinct regions of the brain (Babaeeghazvini et al., 2021). The notion behind this connectivity approach is that areas are presumed to be coupled or are components of the same network if their functional behavior is consistently correlated with each other (Eickhoff and Müller, 2015). In this section, we will first discuss functional connectivity with the amygdala in ASD, and then broader functional connectivity beyond the amygdala. We will discuss the factors that can account for the atypical functional connectivity in ASD, and we will end this section by highlighting novel analytical tools that can effectively detect abnormal functional connectivity in ASD.

3.1. Functional connectivity with the amygdala

Studies have shown abnormal connectivity between the amygdala and visual cortices (Kleinhans et al., 2008) and between the amygdala and the prefrontal cortex (PFC) (Ibrahim et al., 2019; Odriozola et al., 2019) in ASD. Of particular interest is the connectivity between the PFC and the amygdala. Both the PFC and amygdala are critical components of the “social brain” (Stanley and Adolphs, 2013) and both brain regions be pathological in autism (Amaral et al., 2008). There are dense reciprocal anatomical connections between the PFC and the amygdala as seen in non-human primates (Amaral and Price, 1984). In humans, connections between these brain regions have been linked to reduced habituation after repeated presentations of faces in children with ASD (Swartz et al., 2013). Furthermore, children with ASD show reduced amygdala-prefrontal functional connectivity when viewing emotional faces (Ibrahim et al., 2019) and when at rest (see (Hull et al., 2017) for a review), as well as abnormal structural connections (Gibbard et al., 2018). A theoretical account is that the amygdala orchestrates cognitive processes based on social stimuli, but it requires information conveyed from the PFC about the context in which those stimuli occur. In the absence of such contextual input, the amygdala may inappropriately interpret social stimuli (Adolphs, 2010). Together, abnormal connections between the amygdala and PFC may underlie social deficits in autism that cascade beyond facial processing to include processing of other socially relevant stimuli.

It is worth noting that abnormal amygdala-PFC connectivity has broader clinical implications and may not be specific to ASD. For example, abnormal amygdala-PFC effective connectivity to happy faces differentiates bipolar from major depression (Almeida et al., 2009), and increased connectivity between the amygdala, especially the basolateral amygdala, and distributed brain systems (including the PFC) involved in attention, emotion perception, and regulation is associated with high childhood anxiety (Qin et al., 2014).

3.2. Atypical brain connectivity in ASD beyond the amygdala

Traditional wisdom in fMRI studies counts on cognitive tasks to active hemodynamic responses in the brain, which indirectly measure neuronal activity. Earlier studies have shown reduced activation in brain areas of people with ASD associated with face-processing (Kleinhans et al., 2008), working memory (Koshino et al., 2008), and theory of mind (Baron-Cohen et al., 1999). Later, the research focus shifted from a single brain region to activation-driven interregional BOLD correlations (Müller et al., 2011). Most cognitive tasks in those studies have

identified impairments in people with ASD. Therefore, there has been a consensus about how alterations in brain connectivity reflect an ineffective use of neural resources, which leads to impaired coordination in the modulation of task-driven activation among brain regions in ASD.

Atypical functional connectivity (a.k.a., disrupted connectivity (Maximo et al., 2014)) can be broadly classified into two categories: under-connectivity (Just et al., 2012) and over-connectivity (Courchesne and Pierce, 2005). In the former category, reduced functional connectivity has been found across different brain regions in people with ASD for various cognition tasks, including sentence comprehension (Just et al., 2004), visual imagery and language (Kana et al., 2006), problem-solving (Just et al., 2007), response inhibition (Kana et al., 2007), working memory (Koshino et al., 2005), emotional processing (Rudie et al., 2012), and visuospatial attention (Agam et al., 2010). Evidence of under-connectivity has also been found in resting-state fMRI studies (i.e., no cognitive task is involved) (Cherkassky et al., 2006; Di Martino et al., 2013) (see (Hull et al., 2017) for a review). The above studies primarily demonstrate the weaker connectivity between the PFC and relatively posterior brain areas. Other studies have reported under-connectivity in brain areas outside the frontal-posterior network; however, since those findings cover a wide range of brain areas across different tasks, it is often challenging to identify a common pattern of under-connectivity. Indeed, a complete theory about how the social and attentional deficits in autism can be explained by poor connectivity among social brain regions - the amygdala, PFC, and superior temporal sulcus and gyrus (STG) - has remained elusive.

In the latter category, enhanced cortical connectivity or over-connectivity has been reported in several brain regions including the amygdala, extrastriate cortex (Di Martino et al., 2011), frontal and temporal regions, and parahippocampal gyri (Maximo et al., 2014). In particular, the relationship between frontal lobe abnormality and ASD has been revealed (Courchesne and Pierce, 2005), which shows local over-connectivity but long-distance disconnection. Enhanced local but reduced long-distance reciprocal activity and coupling could damage the frontal lobe's function in integrating sensory information. Along this line of reasoning, developmental disconnection syndrome (Geschwind and Levitt, 2007) often helps explain enhanced perceptual functioning (Motttron et al., 2006), impaired face processing (Jemel et al., 2006), and attention deficit (Fair et al., 2007) in autism.

It is worth noting the subtle relationship between under-connectivity and over-connectivity. For instance, it has remained unknown whether local frontal and parietal over-connectivity are the consequence or the cause of global frontal-parietal under-connectivity (Just et al., 2012). It is also worth noting that the fundamental assumption behind task-driven studies is that the baseline connectivity in ASD and typically developing (TD) individuals is equal, which calls for calibration.

An alternative approach to study baseline connectivity is to use task-free resting-state fMRI (Van Den Heuvel and Pol, 2010). Similar findings of under-connectivity in the anterior-posterior connections have been reported (Cherkassky et al., 2006). Another interesting line of research deals with the functional connectivity integrity of the default mode network (DMN) (Assaf et al., 2010; Lynch et al., 2013; Washington et al., 2014). The DMN's uniqueness is reflected by its active role during passive resting states and cognitive processes related to social deficits in ASD.

3.3. Factors affecting atypical brain connectivity

After identifying atypical brain connectivities in ASD, it is natural to probe into the underlying factors affecting disrupted connectivity (toward understanding the etiology of autism). Here, we highlight an anatomical factor (i.e., spatial distance and axonal fiber quality) and a developmental factor (i.e., heterogeneity and trajectory).

It has been hypothesized that spatial distance between brain areas plays a critical role in understanding the functional interaction between them (Tononi et al., 1994). For example, an fMRI study with

problem-solving (Newman et al., 2003) has shown that high-level perception and planning involve two spatially distant areas, the dorso-lateral prefrontal cortex and inferior parietal lobule, but such long-distance connections are disrupted in people with ASD (Just et al., 2007). Meantime, it has also been found that ASD-related behavioral symptoms may be related to decreased long-distance/global connections and increased short-distance/local connections in the brain (Courchesne and Pierce, 2005). One plausible explanation for abnormal local connectivity in ASD is the persistence of glial activation into postnatal life, which often causes the brain of children with autism to grow larger than normal (Courchesne and Pierce, 2005). Such enlargement in brain volume will result in excessive neuronal production such as numerous cortical minicolumns. Increased density of minicolumns would be associated with abnormally enhanced excitatory cortical function. An imbalanced excitation/inhibition ratio has been connected with autism in several studies (e.g. (Rosenberg et al., 2015)).

One possible way of reconciling the discrepancies between findings of autism-related over-connectivity and under-connectivity is to take developmental changes into account (Uddin et al., 2013). As vividly demonstrated in (Uddin et al., 2013), there exist two possibilities for explaining the developmental shift from over-connectivity in children with ASD to under-connectivity observed in adolescents and adults with ASD. To reconcile these findings, it is necessary to collect longitudinal data for the developmental period of puberty (Blakemore, 2012; Casey et al., 2008; Crone and Dahl, 2012). Earlier studies along this line of research have speculated that excessive neuron numbers might lead to early brain overgrowth responsible for disrupted connectivity (Courchesne et al., 2007). In (Courchesne et al., 2011), age-specific changes were measured to highlight anatomic abnormalities in autism such as early brain overgrowth in infancy and the toddler years followed by an accelerated decline in size from adolescence to adulthood. More recently, studies using longitudinal magnetic resonance imaging (MRI) have provided more evidence for an anomalous developmental trajectory of the ASD brains when compared with TD ones (Hua et al., 2013). In (Moseley et al., 2015), global under-connectivity has been shown as an endophenotype of ASD in adolescence, which implies the heritable similarities between ASD adolescents and their relatives. Most recently, complex developmental trajectories were observed for different brain regions, with a developmental peak around adolescence (Van Rooij et al., 2018). These recent findings suggest a persistent interplay in the abnormal development of different brain regions in ASD across the lifespan.

3.4. Network-level tools analyzing atypical functional connectivity

As more autism-related neuroimaging data become publicly available, systematic analysis of anatomical tracts and functional associations at the network level has attracted increasing attention in recent years (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010). Unlike factor analysis, complex network modeling of brain connectivity enables us to borrow a rich set of tools from graph theory to analyze the structural and functional properties of the human brain. An important novel insight provided by the recently developed dynamic functional connectome (Preti et al., 2017) is the paradigm shift from stationary analysis to the dynamic behavior of functional connectivity. In this section, we will first review the general network measures and tools for dynamic functional connectivity and then highlight recent findings directly related to atypical functional connectivity in ASD.

As summarized in (Preti et al., 2017), there are in general two classes of analytical strategies for dynamic functional connectivity: sliding-window correlation and frame-wise analysis. In the former category, connectivity between brain regions is represented by the Pearson correlation between pairs of BOLD sequences (Kucyi and Davis, 2014). Such computation is repeated iteratively by shifting the window to generate a sequence of connectivity measures. Conducting such a procedure for all connections between different brain regions will

produce one connectivity matrix for each specific time (Calhoun et al., 2014). Then the dynamic characterization of whole-brain connectivity boils down to a sequence of connectivity matrices, which support dynamic graph analysis (Mucha et al., 2010). Various matrix factorization techniques can be applied to extract the states of dynamic functional connectivity (Damaraju et al., 2014). In the latter category, an alternative framework based on frame-wise analysis proposes to only retain BOLD signals exceeding a threshold (Tagliazucchi et al., 2012). The frame-wise analysis leads to the generation of voxel-wise brain states (Allen et al., 2014), which can be further analyzed by k-means clustering and principal component analysis (Leonardi et al., 2013). More recently, single-frame analysis has evolved into point process analysis (PPA) and more realistic and precise temporal modeling of state transitions (Guidotti et al., 2015; Majeed et al., 2011).

Analysis of dynamic functional connectivity has shed valuable insights into clinical applications such as Alzheimer's disease (AD) (Greicius et al., 2004), schizophrenia (SZ) (Du et al., 2016), and autism (Koshino et al., 2005). In (Price et al., 2014), dynamic connectivity features are combined in a multi-network and multi-scale approach to improving the classification accuracy of childhood autism. It has been shown that integrating multiple networks across multiple dynamic scales leads to a significant performance improvement. In a more recent work (Wee et al., 2016), a novel framework analyzing short-term activation patterns of brain connectivity was developed to detect the subtle disruptions induced by diseases such as ASD. To reduce significant inter-subject variability, a group-constrained sparse regression model was constructed to weight the corresponding Pearson correlation network. At least 7% accuracy improvement was achieved on the publicly available autism dataset ABIDE (Di Martino et al., 2013). Recently, atypical functional connectivity transitions between sensory and higher-order default mode regions have been demonstrated in a large cohort of participants with ASD relative to controls (Hong et al., 2019).

3.5. Methodological challenges for neuroimaging

Given that a large literature on functional connectivity in autism is based on neuroimaging, we would like to note several methodological limitations of neuroimaging.

First, it is well known that the susceptibility-induced field gradients (SFGs) cause severe dropout of signal in the frontal orbital and lateral parietal brain regions due to the difference in magnetic susceptibility of tissue and air (Glover and Law, 2001). Therefore, caution is needed when analyzing and interpreting data involving the amygdala, which may be susceptible to MRI signal dropouts and have a lower signal-to-noise ratio (SNR) in fMRI.

Second, compared to neurotypicals, it may be more challenging for participants with ASD to remain still in the MRI scanner so participants with ASD may have more head motion artifacts. In a diffusion-weighted MRI (DW-MRI) study, spurious group differences can be attributed to head motion artifacts (Yendiki et al., 2014). In resting-state fMRI, small head motions can produce spurious but structured noise in brain scans, causing distance-dependent changes in signal correlations (Power et al., 2015). In particular, it has been shown that many differences in white matter tracts previously attributed to autism may be attributable to motion artifacts (Power et al., 2015). Therefore, it is important to evaluate head motion for each participant and take head motion artifacts into consideration when comparing between participants with ASD and controls. Accordingly, techniques on motion correction have been developed to compensate motion-related artifacts in resting-state fMRI data (Power et al., 2014).

Third, a primary challenge in neuroimaging studies has been replicating associations between inter-individual differences in brain structure or function and complex cognitive or mental health phenotypes (Marek et al., 2022). The median neuroimaging study sample size is about 25, which is potentially too small for capturing reproducible brain-behavioral phenotype associations (Button et al., 2013), and

smaller than expected brain-phenotype associations and variability across population subsamples can explain widespread replication failures (Marek et al., 2022). Therefore, the impact of sample size on reliability and generalizability (not specific to ASD or the amygdala) should be considered.

3.6. Summary

In summary, a role for pathology involving any single structure, such as the amygdala, seems initially hard to reconcile with the popular view of autism as a disorder of connectivity throughout the brain (Geschwind and Levitt, 2007). A network view may therefore be more appropriate (Stanley and Adolphs, 2013) as it is plausible that abnormal connections at a local network level between the amygdala and other brain regions may explain the impaired social behavior in ASD.

4. New opportunities arising from multimodal neuroimaging with data fusion

As mentioned above, existing literature on atypical functional connectivity has been largely inconsistent with conflicting reports about under-connectivity and over-connectivity (Mash et al., 2018). Such discrepancies are partly due to different neuroimaging modalities such as fMRI, diffusion tensor imaging (DTI), EEG, and magnetoencephalography (MEG). In addition to varying measures of functional connectivity (e.g., BOLD vs. electrical activity), different modalities have their unique strengths and weaknesses concerning spatial and temporal resolution as well as various uncertainty factors (e.g., vulnerability to artifacts). Given the fundamental limitations of unimodal neuroimaging for ASD, multimodal integration of fMRI, EEG, and MEG data holds the potential of resolving discrepancies and providing a unified framework for interpreting experimental findings (Hasan et al., 2013; Libero et al., 2015; Mueller et al., 2013; Yerys and Herrington, 2014). In particular, multimodal neuroimaging and data fusion can facilitate the analysis of transient states of dynamic functional connectivity (Mash et al., 2019), which can capture complex spatiotemporal neural patterns in ASD.

4.1. EEG power and BOLD activity/connectivity

In the literature, the relationship between EEG/MEG signals and neural activities is well understood (da Silva, 2013). By contrast, the BOLD signal, as a secondary hemodynamic measure of neural activities, has not been thoroughly studied (Hillman, 2014). Existing studies about the relationship between BOLD and physiological signals such as intracranial recordings and EEG/MEG have shown that BOLD changes are more closely associated with local field potentials (LFP) than multiunit activity (MUA) (Logothetis et al., 2001). Later, it was found through analyzing the spiking of single neurons that both BOLD and EEG/MEG reflect the synaptic activity of the regional population instead of specific neurons (Mukamel et al., 2005; Nir et al., 2007). The modulatory relationship between cortical oscillations at different frequencies is correlated with both BOLD activity and connectivity. For instance, MEG studies have shown disrupted alpha-gamma phase-amplitude coupling among people with ASD both at rest (Berman et al., 2015) and while viewing faces (Khan et al., 2013). Under the context of ASD research, a recent study has shown atypical lag structure using the so-called resting-state lag analysis (RS-LA) (Mitra et al., 2015).

Existing EEG-fMRI studies have specifically focused on the relationships between EEG power and two types of fMRI measurements: local BOLD fluctuations (a.k.a., “BOLD activity”) and global correlations across different regions (a.k.a., “BOLD connectivity”). It has been reported that the degree of abnormal EEG alpha power and BOLD activity in ASD individuals is highly correlated with behavioral measures obtained from ASD diagnosis (Mash et al., 2020). This line of research suggests that disrupted propagation of intrinsic activity could directly contribute to atypical brain functions in ASD. The relationship between

EEG power and interregional BOLD correlations has also shed valuable new insights into atypical functional connectivity in ASD (Mash et al., 2020). It has been shown that while TD children often show consistently positive relationships between EEG alpha power and regional BOLD power, these associations tend to become weak or even negative in people with ASD. These recent findings of atypical links between alpha rhythms and regional BOLD activity may imply that neural substrates and processes that coordinate thalamocortical regulation of the alpha rhythm are different for ASD.

4.2. Multimodal approach towards transient connectivity states

A novel data-driven strategy for studying transient brain states is to assume that neural networks dynamically fluctuate between a fixed number of replicable connectivity patterns (states or microstates) (Khanna et al., 2015). Temporally clustered microstates can be combined with hemodynamic response function (HRF) (Lindquist et al., 2009) to predict BOLD activation by standard linear regression models (Britz et al., 2010; Musso et al., 2010). EEG microstates can also be used to predict thalamic BOLD fluctuations (Schwab et al., 2015) and BOLD correlation patterns (Olbrich et al., 2009). These studies seem to suggest that transient EEG patterns have a direct relationship with cognitive states of the mind (Milz et al., 2016) and whole-brain BOLD temporal dynamics (Michel and Koenig, 2018). However, it has also been found that each EEG microstate does not necessarily correspond to a unique BOLD resting-state network. For example, some BOLD networks can be simultaneously related to several EEG microstates as shown by (Yuan et al., 2012). Recently, overlapping windows of BOLD sequences are clustered into seven states, each of which corresponds to a unique EEG spectral signature (Allen et al., 2018). As of today, multimodal approaches have not been applied to ASD research. How to leverage multimodal approaches into dynamic functional connectivity transitions is a promising research direction. We will discuss some ideas along this line of research below.

4.3. Multimodal data analysis and integration

Multimodal data analysis and integration have received increasingly more attention from several technical fields including neuroimaging and neurocomputing (Liu et al., 2015; Tulay et al., 2019). Several excellent review articles have already appeared in the literature (e.g. (Sui et al., 2012; Uludağ and Roebroeck, 2014; Zhang et al., 2020)). Here we will highlight the latest advances in multimodal data fusion under the framework of ASD. First, the acquisition of multimodal neuroimaging data can be simultaneous or asynchronous. Simultaneous recording of EEG and fMRI has the advantage of reducing participants' attrition (Goldman et al., 2002; Ullsperger and Debener, 2010); while asynchronous acquisition is more cost-effective and less susceptible to participant discomfort (Babiloni et al., 2004; He and Liu, 2008). Second, the integration of multimodal data can take model-driven or data-driven approaches. Model-driven approaches aim at predicting the relationship between neural activity and neuroimaging data (Valdes-Sosa et al., 2009); however, they have to rely on assumptions about neurovascular coupling whose mechanism has remained partially understood (Rosa et al., 2010). Data-driven approaches do not require *a priori* models characterizing the relationship between neuroimaging data and underlying neural activities (Sui et al., 2012), but their results suffer from a lack of interpretability. This is a particularly important issue because of deep learning for multimodal data fusion (Gao et al., 2020). Third, it has remained an open question whether different modalities should be treated with equal priority. Depending on the application domain, we can formulate either a symmetric or asymmetric analysis of multimodal data.

More specifically, the integration of EEG and fMRI data has taken three different approaches: 1) EEG-informed fMRI; 2) fMRI-informed EEG, and 3) EEG-fMRI fusion. The first two belong to asymmetric

analysis while the last is symmetric. In the first category, EEG-informed fMRI aims at temporal prediction, i.e., predicting BOLD activity from EEG data (Abreu et al., 2018). Both univariate and multivariate methods have been developed to extract EEG features to facilitate the prediction of BOLD signal changes (Abreu et al., 2018). In the second category, fMRI-informed EEG differs in the objective of spatial localization, i.e., fMRI is exploited to improve the source localization of EEG (Ou et al., 2010). As shown by (Lei et al., 2015), fMRI data can substantially improve the accuracy of EEG source localization. Accordingly, fMRI-informed EEG can be used to characterize multimodal network connectivity, which could help describe the interactions among these networks (Lei et al., 2011). In the third category, model-based EEG-fMRI fusion methods such as (Daunizeau et al., 2007; Sotero and Trujillo-Barreto, 2008; Valdes-Sosa et al., 2009) often assume *a priori* biophysical models (e.g., neural mass model and metabolic hemodynamic model) to link BOLD signals with neural activity. Data-driven EEG-fMRI fusion includes joint independent component analysis (ICA) (Moosmann et al., 2008), parallel ICA (Eichele et al., 2008), and canonical partial least squares (Michalopoulos and Bourbakis, 2015).

4.4. Summary

In summary, multimodal neuroimaging and data fusion can facilitate the analysis of transient states of dynamic functional connectivity, which in turn provides a great opportunity to capture complex spatiotemporal neural patterns in ASD. Applying multimodal approaches to dynamic functional connectivity transitions is an under-explored area in autism research, and there is still plenty of room for combining model-based and data-driven approaches for EEG-fMRI fusion, especially given rapid advances in machine learning in recent years (Tu, 2020).

5. New opportunities with human single-neuron recordings

Another under-explored opportunity in autism research is to employ human single-neuron recordings to study the neural circuits underlying atypical social behavior in ASD. Human single-neuron recordings provide a very unique and valuable opportunity to directly study cognition at the neuronal level in the human brain. Neurosurgical patients being treated for intractable epilepsy have the opportunity to volunteer to participate in research (Fried et al., 2014). Based on the high co-morbidity between autism and epilepsy (ca. 20%) (Sansa et al., 2011), it is likely to recruit neurosurgical patients with ASD. In particular, human single-neuron recordings have a major focus on the medial temporal structures including the amygdala (Fried et al., 2014; Rutishauser et al., 2015), allowing researchers to test important hypotheses in autism research. For example, our first publication on directly recording single neurons in people with ASD has shown that amygdala neurons are atypically tuned to facial features (Rutishauser et al., 2013). With the highest possible spatial and temporal resolution currently available, human single-neuron recordings can have a significant impact on autism research.

Importantly, a state-of-the-art human single-neuron recording setup is able to simultaneously record single neurons and LFPs from multiple brain regions, which is especially useful for functional connectivity analysis. Therefore, single-unit recordings will not only provide a level of temporal and spatial acuity missing in neuroimaging data but also help distinguish between stimulus-driven vs. goal-driven modulating processes, making possible the isolation of specific neural processes that may be especially abnormal in ASD. In particular, with detailed and comprehensive functional connectivity analysis, we can test many important hypotheses that cannot be answered by neuroimaging approaches. For example, is the coding of faces in the PFC supported by its functional connectivity with the amygdala? Given that the amygdala is highly involved in face processing (Adolphs, 2008; Rutishauser et al., 2015), the amygdala may provide critical information about faces to the PFC. Furthermore, are social attentional signals in the amygdala

modulated by input from the PFC? In addition to the attentional signals related to target detection in the amygdala (Wang et al., 2018) and PFC (Wang et al., 2019), it has been shown that the amygdala is critical for visual attention to faces (Adolphs et al., 2005; Wang and Adolphs, 2017b) and PFC lesions in humans lead to impaired social attention (Vecera and Rizzo, 2004). Therefore, the amygdala and PFC may form a reciprocal network that encodes social attention. These observations are all highly related to the social dysfunctions in ASD (e.g., impaired face processing and impaired social attention). It is thus important to understand whether social dysfunctions in ASD can be attributed to abnormal amygdala-PFC functional connectivity at the neural circuit level.

In summary, direct recording from neurosurgical patients with ASD is an emerging opportunity to understand the neural mechanisms underlying atypical social behavior in ASD at the single-neuron and neural circuit levels. Comprehensive functional connectivity analysis can elucidate details of the neural circuits underlying social deficits in autism, especially the amygdala-PFC circuit. The unique opportunity to record directly from neurons in the human brain will bridge the gap between standard neuroimaging techniques that lack this level of spatial and temporal resolution and neurophysiological studies of non-human animals. With human single-neuron recordings, we are able to test important hypotheses about how the amygdala is involved in autism and reconcile previous neuroimaging and lesion findings. Therefore, the significance of recording single-neuron data in people with ASD is extremely high.

6. Conclusions

In this article, we have reviewed the development of studies using an array of cognitive tasks to investigate the functional role of the amygdala in ASD for the past two decades. Direct comparisons between people with ASD and amygdala lesion patients using the same tasks indicate that the amygdala can only account for some deficits in face processing but not visual attention (neither top-down nor bottom-up) in ASD. Studying functional connectivity with the amygdala in ASD suggests that a role for pathology involving any single structure, such as the amygdala, seems initially hard to reconcile with the popular view of autism as a disorder of connectivity throughout the brain. By contrast, it is more plausible that abnormal connections at a local network level between the amygdala and other brain regions may explain the impaired social behavior in ASD. To experimentally test this hypothesis, multimodal neuroimaging and data fusion can facilitate the analysis of transient states of dynamic functional connectivity, which in turn provides a great opportunity to capture complex spatiotemporal neural patterns in ASD. The unique opportunity to record directly from neurons in the human brain will bridge the gap between standard neuroimaging techniques that lack this level of spatial and temporal resolution and neurophysiological studies of non-human animals. The explosion of multimodal neuroimaging data, including single-neuron recordings, is expected to elucidate details of the neural circuits underlying social deficits in people with ASD in the future.

Author contributions

S.W. and X.L. contributed equally to the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

This research was supported by the AFOSR (FA9550-21-1-0088), NSF (BCS-1945230, IIS-2114644), NIH (R01MH129426), and Dana Foundation. The funders had no role in the decision to publish or preparation of the manuscript.

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