

## “Salience network” dysfunction hypothesis in autism spectrum disorders

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**Abstract:** Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social interaction and communication, as well as repetitive and stereotyped patterns of behavior. Although most patients with ASD show sensory abnormalities such as hyperesthesia and hypoesthesia, its relation to social cognition has not been well studied. Recently, a salience network (SN) dysfunction hypothesis of ASD has been proposed. This neuroscientific hypothesis might explain how a SN integrating external sensory stimuli with internal states mediates interactions between large-scale networks involved in externally and internally oriented cognitive processing. In the brain of patients with ASD, areas of the SN, including the anterior insula, become dysfunctional, which results in difficulty in operating social cognition and self-referential processing. Here we discuss the controversial points and future directions of this hypothesis.

**Key words:** autism spectrum disorder, salience network, executive control network, default mode network.

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Autism spectrum disorder (ASD) is a developmental disorder characterized by social deficits, communication difficulties, and stereotyped or repetitive behaviors and interests. This disorder is characterized by atypical social interaction (i.e., lack of attachment, inability to cuddle or to form reciprocal relationships, or avoidance of eye gaze), insistence on sameness (i.e., resistance to change, rituals, intense attachment to familiar objects, or repetitive acts), speech and language problems (ranging from complete muteness to a delayed onset of speech to a markedly idiosyncratic use of language), and uneven intellectual performance. Currently, ASD is diagnosed using the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) or the International Classification of Diseases (ICD)-10. These diagnostic criteria have many common items associated with difficulty in social skills. Diagnosis is made clinically and usually requires evidence of impair-

ment in social interaction and communication, as well as the presence of restricted, repetitive, stereotyped behaviors or interests.

In ASD, there is considerable individual variation of social function and other skills such as intellectual ability. Patients with ASD usually exhibit significant language delays and social and communication challenges. Many patients with ASD also have intellectual disabilities. Individuals with Asperger syndrome demonstrate normal intelligence and language development, but exhibit severely impaired social skills. The main difference between ASD and Asperger syndrome is thought to involve language development: Patients with Asperger syndrome will typically not demonstrate delayed language development at young ages. Patients with ASD show a wide range of neuropsychological deficits, independent of their functional level. In particular, cognitive domains such as the ability to mentalize/theory

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of mind, executive functions, central coherences, and procedural learning have been considered major factors in the impairment of social adjustment. In addition, patients with ASD show a wide range of characteristic symptoms (peripheral symptoms), which are not included in the current diagnostic criteria.

In particular, the most observed characteristic symptom in ASD is abnormal sensation (hypersensitivity and hypoesthesia). A large majority of patients with ASD display abnormally subjective sensory experiences in their sensory modalities. Classical work performed by Kanner (1943) demonstrated that children with autism exhibit a strong fear of sound produced by some types of furniture or of trembles inside an elevator; in contrast, other children were unaware of noises that many people might consider very loud. Gillberg and Billstedt (2000) also reported that abnormal responses to sound were prominent in children with autism. For example, a child who seems to be deaf is astonished when he/she unexpectedly hears the sound of a chocolate wrapper being removed, and many children with autism will cover their ears to shut out even "ordinary" noise levels. Abnormal sensory experiences are extended in all sensory modalities in patients with ASD (Gillberg & Billstedt, 2000). To assess abnormal sensation, a Sensory Profile measure has been used internationally (Crane, Goddard, & Pring, 2009; Dunn, 1997; Kientz & Dunn, 1997; Watling, Deitz, & White, 2001). The Sensory Profile may be applied in infants as well as adults, and may reveal life-long sensory problems. Leekam, Nieto, Libby, Wing, and Gould (2007) comprehensively investigated the prevalence of sensory abnormalities in patients with ASD. This study used two types of measure to assess abnormal sensory processing: the sensory items included in the Diagnostic Interview for Social and Communication Disorders (DISCO) and the comparative selective items from the Sensory Profile. More than 90% of patients (children and adults) with ASD with low and high function showed multimodal sensory abnormalities. In Japan, Takahashi and Masubuchi (2008) collected and analyzed episodes of sensory problems from memoranda

written by patients with ASD. They presented 330 episodes of abnormal sensory experiences across all sensory modalities. They reported that patients with ASD felt pain in the rain and while showering. Moreover, patients with ASD could not tolerate noise in a crowd, felt bad when they placed their tongue on any type of food, and were also frightened at the sight of a flooding room.

The sensory problems observed in patients with ASD were not limited to a specific sensory modality and thus should not be attributed to a lesion in a specific sensory organ or sensory cortex in the brain. Although most patients with ASD have sensory problems, both the ICD-10 and the DSM-IV-TR have not defined these problems as a diagnostic requirement. As previously described, very few attempts have been made to identify the relation between social deficits and sensory abnormalities. Several theories have been proposed to contribute to the social deficits and communication difficulties in patients with ASD on the basis of "theory of mind" deficits (Baron-Cohen, 2009), executive function deficits (Kenworthy, Yerys, Anthony, & Wallace, 2008), mirror neuron system dysfunction, and weak central coherence (Happé & Frith, 2006). However, these theories do not include sensory problems. For example, is the sensory problem observed in ASD an independent syndrome of cognitive disorders in cognition and behavior?

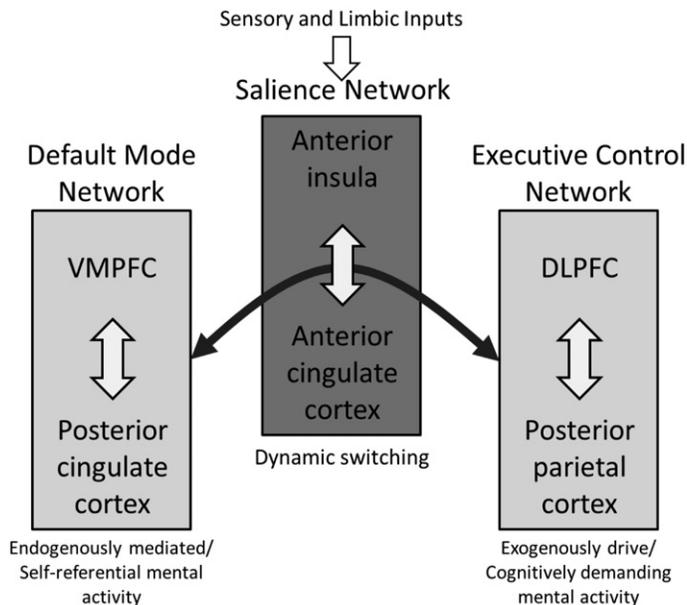
Recently, a new and interesting theory based on neuroimaging studies has been proposed (Menon & Uddin, 2010; Uddin & Menon, 2009). This theory involves the anterior insula (AI), which processes the subjective evaluation and emotional salience associated with the sensory experience that controls the other two neural networks: the executive control network (ECN) and the default mode network (DMN). Several studies have defined the neural network that contributes to subjective evaluation and emotional intensity as the salience network (SN). The SN serves to integrate sensory data with visceral, autonomic, and hedonic information as an interoceptive sensation. The ECN contributes to various cognitive processes associated with executive functions

and social cognition. The DMN contributes to self-referential processing. Uddin and Menon (2009) have previously reported that the SN processes that accompany sensory experiences are primarily deteriorated, which results in a dysregulation of social cognition that is associated with the ECN in ASD.

Therefore, from here on in, we will refer to the theory of Uddin and Menon (2009) as the SN dysfunction hypothesis. The SN dysfunction hypothesis may explain the interaction between sensory problems with a social impairment in ASD, and thus, this hypothesis may represent a fundamental theory compared to other pathophysiological theories. Here, we describe the SN dysfunction hypothesis, which proposes that sensory abnormalities affect social cognition in ASD. First, we will describe this model in more detail, referring to references cited in the work by Uddin and Menon (2009). In addition, we will discuss the evidences in support of this theory, as well as the current status of the field and future directions.

## The salience network dysfunction hypothesis in ASD

The SN dysfunction hypothesis is a neurocognitive model based on a systematic approach that combines findings in the field of neuroanatomy, neurophysiology, and psychology. This hypothesis is based on a model that has successfully described the confluent relations of multiple neural circuits by analyzing the networks between brain regions by using recently developed functional MRI analytical methods. These neural circuits encode the saliency of sensory experiences predominantly associated with the AI, and exclusively control both the DMN, which is associated with self-awareness, and the ECN, which is associated with cognitive processing (see Figure 1). One proposal introduced by Uddin and Menon (2009) describes the SN (particularly the AI) as dysfunctional in ASD and dysregulated in specific cognitive processes that enable adaptation to a social context. Moreover, the AI has many functional



**Figure 1** Model of salience network function illustrated in Uddin and Menon (2009): The anterior insula (AI) is part of a salience network that serves to initiate dynamic switches between the default mode network (DMN) and the executive control network (ECN). In our model of AI dysfunction in autism, limbic and sensory inputs are inadequately processed by the AI during social cognition, leading to disruption of the AI's role in coordination of these large-scale brain networks (Uddin & Menon, 2009, p. 1202, Figure 2).

roles for multimodal sensory processing, emotional cognition, and social cognition, among others. Thus, the SN dysfunction in ASD might be associated with abnormal sensory processing and may secondarily induce atypical cognitive processes, including social cognition. There is a strong expectation that the SN dysfunction hypothesis may become an important pathophysiological hypothesis in ASD. In this section, we take a closer look at the proposal provided by Uddin and Menon (2009) and present supportive evidence from multiple perspectives.

#### *The insular cortex encodes the intensity of sensory experience*

The SN has a neuronal connection with a central focus on the AI. We present several findings of the AI regarding its intensity in sensory experience and its integration in multimodal sensory processing. The insular cortex is located deep within the lateral sulcus between the frontal, temporal, and parietal lobes and processes multimodal and cognitive information, including visceral sensory, visceral motor, vestibular, pain, temperature, language, visual, auditory, and tactile information (Augustine, 1996). The insular cortex encodes the intensity of a sensory experience. Bornhovd, Quante, Glauche, Bromm, Weiller, and Buchel (2002) demonstrated that the response of the insular cortex to a pain stimulus showed a positive linear relation with stimulus intensity. Recently, several studies have discussed that the insular cortex might be “a multimodal magnitude estimator,” similar to a salience detector that triggers subjective evaluation and attention (Baliki, Geha, & Apkarian, 2009; Moayedı & Weissman-Fogel, 2009). In particular, the AI, which is an anterior part of the insular cortex, has been recognized as a center of integration between emotional expression and sensory experience (Kober, Barrett, Joseph, Bliss-Moreau, Lindquist, & Wager, 2008). For example, the insular cortex contributes to the shaping of emotional experience from the bodily state, similar to the autonomic nervous system (Damasio, 1996).

#### *The AI contributes to emotion recognition and social cognition*

A meta-analysis of a great majority of functional neuroimaging studies indicates that the AI is consistently activated during the expression of emotion, including various negative and positive emotions such as anger, sadness, fear, disgust, happiness or joy, trust, and surprise (Kober et al., 2008). It has been recognized that the AI integrates multimodal sensory information and conscious emotional recognition. In the field of social neuroscience, several studies have demonstrated that the AI is involved in the affective component of empathy and social pain, which are processes required to understand another’s emotion by sharing in their own affective states (Bernhardt & Singer, 2012; Jackson, Meltzoff, & Decety, 2005; Singer, Seymour, O’Doherty, Kaube, Dolan, & Frith, 2004). In association with this finding, Singer et al. (2004) showed that while the posterior insula was activated when subjects received painful stimulation, the AI and anterior cingulate cortex were both activated when the subject received pain and when the subject witnessed a loved one receiving pain. The study concluded that the AI constituted a common neural base for our understanding of the feelings of others (empathy) and ourselves. Very few attempts have been made at identifying the neural substrate of emotional recognition in the insular cortex in ASD studies. For example, Silani, Bird, Brindley, Singer, Frith, and Frith (2008) indicated that difficulties in emotional awareness were related to the hypoactivity of the AI in both patients with ASD and typical developmental controls. The poorer the awareness of one’s emotions, as well as the emotions of others, the weaker the activity observed in the AI (Silani et al., 2008). They interpreted this difficulty in emotion recognition as alexithymia and subsequently revealed a correlation between hypoactivity of the AI to emotional stimulus and alexithymic traits (Silani et al., 2008). Alexithymia is a state of deficiency in the understanding of one’s emotions and in the ability to express emotions. Individuals with alexithymia lack the ability to imagine and, despite dwelling on their own situation, they

find it difficult to verbally express the emotions that accompany such situations; this affects their interpersonal relationships. Furthermore, Bird, Press, and Richardson (2011) replicated these findings and demonstrated that the response of the AI to social pain was correlated with the degree of alexithymia, but was not an autistic trait.

In conclusion, the AI contributes to an integrated emotional awareness based on multimodal sensory information and applies these common neural substrates to understand one's and other's emotional state. The degree of evaluating the intensity of a sensory experience in the AI might affect the cognitive aspects of causal attribution in the emotional state and subsequently contribute to one part of the difficulty in empathizing faced by patients with ASD.

#### *Supportive evidence for dynamic switching of the SN*

The SN, which Uddin and Menon (2009) had initially proposed, consists of mainly the AI and anterior cingulate cortex, which was identified by a network analysis using fMRI. Seeley, Menon, Schatzberg, Keller, Glover, Kenna, Reiss, & Greicius (2007) conducted independent component analyses of resting-state fMRI data and extracted an independent brain network consisting of the AI, anterior cingulate cortex, and subcortical structures, including the amygdala, substantia nigra / ventral tegmental area, and thalamus. Uddin and Menon (2009) called this network the SN on the basis of the functional role of the AI. The SN is distinct from the two other large-scale brain networks, ECN and DMN. The SN first evaluates any changes in the physiological homeostasis that occurs as a result of body sensation or other sensory processing and triggers the appropriate adaptive behavior (Eckert, Menon, Walczak, Ahlstrom, Denslow, Horwitz, & Dubno, 2009).

The ECN is a functional integration of brain regions focused on both the dorsolateral prefrontal cortex and the posterior parietal cortex, and is a network involved in various cognitive processes, such as working memory and behavioral control. The ECN has shown a strong

intrinsic functional coupling and strong coactivation during various cognitive tasks associated with information processing cognitive functions, including goal-oriented behavior, and the flexible switching of working memory and problem solving (Koechlin & Summerfield, 2007; Miller & Cohen, 2001; Muller & Knight, 2006; Petrides, 2005).

The DMN is a functional integration focused on the ventromedial prefrontal cortex (VMPFC) and the posterior cingulate cortex (PCC) and is characterized by a coherent neural oscillation at a low frequency rate in the resting state (Deco, Jirsa, & McIntosh, 2011). The precise functions of the DMN are still largely unknown; however, the individual brain regions comprising it are hypothesized to be involved in the integration of autobiographical, self-monitoring, and related social cognitive functions (Spreng, Mar, & Kim, 2009). The DMN includes the medial temporal lobes, angular gyrus, the PCC, and the VMPFC. The PCC is activated during tasks that involve autobiographical memory and self-referential processes (Buckner & Carroll, 2007); the VMPFC is associated with social cognitive processes that are related to self and others (Amodio & Frith, 2006); the medial temporal lobe is engaged in episodic and autobiographical memory (Cabeza, Prince, Daselaar, Greenberg, Budde, Dolcos, LaBar, & Rubin 2004), and the angular gyrus is implicated in semantic processing (Binder, Desai, Graves, & Conant, 2009). During the performance of cognitively demanding tasks, the ECN typically shows increases in activation, whereas the DMN shows decreases in activation (Greicius, Krasnow, Reiss, & Menon, 2003; Greicius & Menon, 2004; Raichle, MacLeod, Snyder, Powers, Gusnard, & Shulman, 2001). As the activation of the DMN temporally fluctuates with a negative correlation to signals from within the region that includes the network stimulated during cognitive problem solving, the DMN and the ECN might contribute to different aspects of both social and nonsocial cognitive processing. Currently, the DMN has garnered much attention in different fields and is being extensively studied in areas including

psychology, neuroscience, and psychiatry (Broyd, Demanuele, Debener, Helps, James, & Sonuga-Barke, 2009). Among these studies, ASD studies have shown multiple cases of reduced DMN activity (Ebisch, Gallese, Willems, Mantini, Groen, Romani, Buitelaar, & Bekkering, 2011). According to Assaf, Jagannathan, Calhoun, Miller, Stevens, Sahl, O'Boyle, Schultz, and Pearlson (2010), the strength of the DMN integration within cases of ASD has weakened, thereby correlating it with a measure of sociability.

Regarding the integration of the three functional networks described above, studies have found confluent relations between brain regions using recent functional imaging and have shown that the AI is not only stimulated prior to reaching the ECN and the DMN, but is also involved in driving these networks, where the ECN and the DMN are exclusively activated. Sridharan, Levitin, and Menon (2008) have shown that across three independent data sets, the right AI plays a critical and causal role in switching between two other major networks (the ECN and the DMN), which are known to demonstrate competitive interactions during cognitive information processing (Fox, Snyder, Vincent, Corbetta, Van Essen, & Raichle, 2005; Greicius et al., 2003). The study used Granger causality analyses to examine the directionality of the effect of the AI and anterior cingulate cortex nodes of the SN on other brain regions. Granger causal analyses enabled the detection of causal interactions between brain regions by assessing the extent to which signal changes in one brain region can predict signal changes in another brain region (Goebel, Roebroeck, Kim, & Formisano, 2003). Across stimulus modalities, the right AI plays a critical and causal role in activating the ECN and deactivating the DMN (Sridharan et al., 2008). This study also showed that the right AI is involved in switching between brain networks across task paradigms and stimulus modalities, and thus acts as a causal outflow hub that coordinates between two major large-scale networks. Latency analysis, which includes measures of the time to peak, further confirmed that the right AI activity temporally precedes the

activity in the other nodes of the ECN and the DMN. This new understanding of the right AI as a critical node for initiating network switching provides a key insight into the core functions of the AI.

Abnormal SN processing, such as chronic decreased AI activity, may induce an inappropriate neural response and cognitive processing in response to a cognitively challenging task. In ASD, a comprehensive meta-analysis of functional neuroimaging studies of social processing demonstrated that, across a group of studies examining various aspects of social processing, one of the regions that consistently showed a significant hypoactivity in individuals with ASD was the right AI (Di Martino, Ross, Uddin, Sklar, Castellanos, & Milham, 2009). This may underlie the consequence of ineffective salience processing in the AI in response to reduced attention to social stimuli, a hallmark of ASD.

#### *Psychological interpretation of SN dysfunction in ASD*

From a psychological perspective, the SN is a process that motivates coping behavior in response to the environment by evaluating the intensity and saliency of the emotional response associated with sensory experiences. Uddin and Menon (2009) indicated that the SN chronically decreases and does not function to evaluate emotional salience in ASD. Moreover, because of the dysregulation resulting from a switch between the DMN and ECN, patients with ASD cannot execute appropriate coping behavior. Thus, we speculate how the SN dysfunction contributes to the clinical presentation of patients with ASD from a psychological perspective.

As previously mentioned, activation of the AI in response to an emotional stimulus is not always reduced in ASD, but rather reflects an alexithymic trait and difficulty to empathize (Bird et al., 2011; Silani et al., 2008). Although psychological studies have found that the processing of empathy is weaker in patients with ASD compared with neurotypical individuals, the activity of the AI does not predict the degree of the autistic trait. Empathy is divided

between the cognitive processes that deduce the mental state of another individual and the processes of reproducing an emotional state. The AI responds to empathic processing by contributing to the coding of emotional responses, which simulates the state of another person. Thus, understanding one's own emotional state and understanding another individual's emotional state are both processed using common information processing and neural bases. Some studies have called these neural substrates "shared-network" models of empathy (Bird, Silani, Brindley, White, Frith, & Singer, 2010; Preston & de Waal, 2002). Clinically, individuals with ASD show difficulty in understanding the state of another individual and even have difficulty in understanding themselves. Alexithymia is a state of deficiency in the understanding of one's own emotions and in the ability to express these emotions. Alexithymia was originally thought to predominantly exist in patients with somatoform disorder; however, the difficulty in self-emotional awareness is relevant to ASD. An assessment of alexithymia is generally conducted using a self-report questionnaire known as the 20-item Toronto Alexithymia Scale (TAS-20; Bagby, Parker, & Taylor, 1994; Bagby, Taylor, & Parker, 1994). There have been a few studies using the TAS-20 in which patients with ASD have demonstrated a high tendency to exhibit an alexithymic trait (Berthoz & Hill, 2005; Hill, Berthoz, & Frith, 2004). However, these two studies did not quantitatively evaluate the autistic tendency and the correlation with the alexithymic trait was unclear.

An fMRI study conducted by Silani et al. (2008) also used the TAS-20 questionnaire. They compared the results of individuals with high-functioning autism / Asperger syndrome and a group of neurotypical individuals and revealed that the high-functioning autism / Asperger syndrome group demonstrated a higher tendency toward alexithymia. In addition, the alexithymia tendency of both groups showed a significant correlation with their empathetic abilities, with a negative correlation found in AI-stimulated individuals as assessed using fMRI in subjects viewing an emotion-

evoking slideshow. The AI is involved in the monitoring of emotions, regardless of whether they are one's own or another's emotions, and thus, the AI does not properly function in individuals with ASD because of this fundamental problem. These individuals find it difficult to understand emotions in both themselves and in others.

Thus, the activity of the AI itself partially contributes to social difficulty in individuals with ASD, and the neural network (SN), including the AI, dynamically affects various aspects of social cognition. There is a strong expectation that hypoactivity of the AI contributes to difficulties in emotion recognition such as alexithymia, which is not an autistic trait, and the subsequent SN dysfunction induces a comprehensive autistic clinical representation due to a dysregulated ECN and/or DMN. From a psychological perspective, the SN dysfunction hypothesis may support hierarchical processes for emotion recognition.

## Future directions

The SN dysfunction hypothesis is a pathological hypothesis of extreme interest when explaining the deviated nature of sensory processing and cognitive function found in ASD. Despite this, Uddin and Menon (2009) did not discuss the various psychological and neurophysiological problems observed in ASD. Thus, further studies are needed to test this hypothesis from a cross-sectional perspective. In this section, we introduce several research topics to clarify the relation between sensory abnormalities and SN dysfunction in ASD.

According to the SN dysfunction hypothesis, the SN is responsible for controlling the ECN and DMN; however, the SN itself is also a process that occurs in accordance with sensory experiences and does not occur in lower-order sensory areas. Sensory experiences are transmitted from the sensory organs to lower-order sensory areas, which are then projected to the insula via higher-order association brain regions. Many different ASD studies have recently shown abnormalities in the processing

of initial perceptions associated with sensory experiences prior to reaching the insular cortex. There have also been several reports of insufficient neural responses to sensory stimuli in primary sensory areas among multiple sensory modalities.

Evoked potential recordings obtained using EEGs are indicators of a neural response to sensory stimuli in sensory areas or in neural circuits terminating in sensory areas. There are several evidences of somatosensorily evoked, auditorily evoked, and visually evoked potentials in patients with ASD. In studies of somatosensorily evoked potentials in children diagnosed with autism between the ages of 2 and 9 years, approximately half of the children showed a delay in peak latencies of specific components and abnormal increases in amplitude (Miyazaki, Fujii, Saijo, Mori, Hashimoto, Kagami, & Kuroda, 2007). For example, one study investigated a comparatively large number of cases using auditorily evoked potentials to examine auditory brain stem responses that evaluated the nerve responses of neural circuits in response to auditory processing (Rosenhall, Nordin, Brantberg, & Gillberg, 2003). In this study, individuals with autism that developed during childhood or adolescence showed significant abnormalities in a number of components compared with the corresponding neurotypical group. Furthermore, during an examination of auditorily evoked magnetic fields using MEG to detect neural responses in the auditory cortex of the temporal lobe, the M100 component in response to pure-tone stimuli was severely delayed in individuals with ASD, which correlated with both IQ and language function (Roberts, Khan, Rey, Monroe, Cannon, Blaskey, Woldoff, Qasmieh, Gandal, Schmidt, Zarnow, Levy, & Edgar, 2010).

Recently, a neuroimaging study has shown that a neural response to sensory stimuli varies from moment to moment, and that perceptual processing might abnormally fluctuate. Dinstein, Heeger, Lorenzi, Minshew, Malach, and Behrmann (2012) measured fMRI responses to visual, auditory, and somatosensory stimuli and found that the trial-by-trial response reliability was significantly weaker in

patients with high-functioning autism. They concluded that cortical responses in ASD showed smaller signal-to-noise ratios in all of the sensory systems. In addition, studies using EEG/MEG have suggested a similar conclusion regarding cortical dysfunction in ASD. EEG/MEG results have provided measures of neural synchronization, such as event-related synchronization or phase-locking factors, unlike evoked responses from averaging. In particular, the phase-locking factor represents the consistency of cortically evoked responses to sensory stimuli among a number of trials. A recent MEG study in children with ASD demonstrated a reduction in the gamma frequency phase-locking factor in response to auditory stimuli (Gandal, Edgar, Ehrlichman, Mehta, Roberts, & Siegel, 2010). In adults with ASD, the gamma frequency phase-locking factor was also reduced compared with controls (Rojas, Maharajh, Teale, & Rogers, 2008). Interestingly, the resting state gamma oscillation was abnormally enhanced in patients with ASD (Orekhova, Stroganova, Nygren, Tsetlin, Posikera, Gillberg, & Elam, 2007). Similar findings have been replicated in patients with schizophrenia and in animal models of autism. Abnormal enhancements of resting gamma activity and its reduction in perceptual tasks have been reported in studies of schizophrenia, suggesting abnormally lower sensory processing associated with psychotic symptoms (Gandal, Edgar, Klook, & Siegel, 2011; Uhlhaas & Singer, 2010). Therefore, abnormal ongoing cortical fluctuations cause alternations in perception and/or habituation, thus affecting subjective sensory and emotional experiences independent of SN dysfunction.

Taken together, the combination of these findings and information indicates that problems in neural development exist from the onset of ASD, in which atypical sensory processing results from organic problems, including those found in the structure of neural connections between sensory organs and the sensory cortex, in the cell structure of the sensory cortex, and in the various neural connections between the sensory cortices and lower brain regions. As the SN is involved in the

strength of emotional processing and the subjective experience evoked by sensory experiences, the SN may not be directly connected to the initial stages of perception processing. On the basis of this consideration, problems in the coding process of sensory experiences may exist within ASD and occur prior to SN processing, thereby potentially causing abnormal processing to occur secondarily in the SN. However, whether the SN in patients with ASD is independently processing atypically, or whether neural activity involved in the initial sensory experience influences hypersensitivity or hyposensitivity when processing within the SN, remains unclear. Thus, further examination of SN processing from the perspective of temporal processing progression is necessary. Further studies are required to address questions arising from a number of different perspectives.

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