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Sensory processing in autism spectrum disorders and Fragile X syndrome—From the clinic to animal models

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Abstract

Brains are constantly flooded with sensory information that needs to be filtered at the pre-attentional level and integrated into endogenous activity in order to allow for detection of salient information and an appropriate behavioral response. People with Autism Spectrum Disorder (ASD) or Fragile X Syndrome (FXS) are often over- or under-reactive to stimulation, leading to a wide range of behavioral symptoms. This altered sensitivity may be caused by disrupted sensory processing, signal integration and/or gating, and is often being neglected. Here, we review translational experimental approaches that are used to investigate sensory processing in humans with ASD and FXS, and in relevant rodent models. This includes electroencephalographic measurement of event related potentials, neural oscillations and mismatch negativity, as well as habituation and pre-pulse inhibition of startle. We outline robust evidence of disrupted sensory processing in individuals with ASD and FXS, and in respective animal models, focusing on the auditory sensory domain. Animal models provide an excellent opportunity to examine common mechanisms of sensory pathophysiology in order to develop therapeutics.

Keywords

Autism; Sensory filtering; Habituation; Fragile-x; Sensory processing; Startle; EEG; Animal model; Translation

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1. Introduction

We are continuously bombarded with sensory stimuli in daily life. The appropriate pre-attentive filtering of this sensory information and its integration into other cognitive processes are critical for healthy brain function. This is exemplified in autism spectrum disorder (ASD), in which abnormal filtering and the accompanying hyper-sensitivity or hypo-sensitivity to sensory stimuli are cardinal symptoms which have a debilitating impact on social interactions and daily functioning (Crane et al., 2009; Elison et al., 2013; Elsabbagh et al., 2013; Hirstein et al., 2001; Leekam et al., 2007; Minshew et al., 2002; Zwaigenbaum et al., 2005). ASD impacts approximately 1 in 68 children in the US, with nearly five times higher incidence in boys than girls (data from 8 year old children, Autism and Developmental Disabilities Monitoring (ADDM) Network – CDC, 2010). Individuals with ASD display a range of symptoms potentially related to sensory disruptions, including difficulties with social communication/interactions, fixated interests, inflexible routines and motor stereotypies.

Fragile X Syndrome (FXS) is the most common monogenic form of ASD that affects 1 in 4000 males and 1 in 8000 females. FXS occurs due to a mutation in the Fmr1 gene that results in the down-regulation of fragile × mental retardation protein (FMRP). FMRP is a translation regulator and its absence causes abnormal protein synthesis particularly those associated with activity dependent synaptic plasticity. The symptoms of FXS include intellectual disability, repetitive behaviors, social communication deficits, increased anxiety and arousal, and abnormal sensory processing. Between one quarter and one third of individuals with FXS are also diagnosed with ASD (Bailey et al., 2008; Rogers et al., 2001). Several studies suggest the existence of similar pathophysiological and anatomical mechanisms in ASD and FXS, particularly in the sensory processing domain (Belmonte and Bourgeron, 2006; Feinstein and Reiss, 1998; Hagerman, 2006; Pickett and London, 2005; Reiss et al., 1995).

Of all the symptom domains characterizing ASD and FXS, the sensory domain arguably holds the most promise for revealing mechanisms central to the pathogenesis of the spectrum of disorders. Sensory processing difficulties in ASD are manifested in hypersensitivity, avoidance of sensory stimuli, diminished responses to sensory stimulation, and/or sensory seeking behavior. These symptoms can impact multiple sensory systems including the visual, auditory, gustatory, olfactory and tactile systems (Ben-Sasson et al., 2008; Cascio et al., 2015; Foss-Feig et al., 2012; Klintwall et al., 2011; Lane et al., 2014; Liss et al., 2006; Marco et al., 2012; O'Connor, 2012). Similar sensory system deficits are also seen in humans with FXS (Baranek et al., 2008; Castrén et al., 2003; Frankland et al., 2004; Kogan et al., 2004; Miller et al., 1999; Rotschafer and Razak, 2014; Schneider et al., 2013; Van der Molen et al., 2012a,b). The symptoms can be evaluated by clinical assessment or parent report (Baranek et al., 2008; Ben-Sasson et al., 2007; Tavassoli et al., 2016) and have recently been included as a criterion for ASD diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Sensory abnormalities in ASD and FXS are not only among the most replicable features of these disorders (Ben-Sasson et al., 2008; Donkers et al., 2015; Klintwall et al., 2011; Liss et al., 2006), they are also present early in childhood (Baranek et al., 2008; Elison et al., 2013; Elsabbagh et al., 2013; Germani

et al., 2014; Zwaigenbaum et al., 2005) and are strong predictors of some later-emerging symptoms, such as anxiety (Green et al., 2012; Sullivan et al., 2014). Importantly, sensory deficits may be accompanied by neurophysiological abnormalities of sensory processing which can be quantified objectively and non-invasively using electroencephalography (EEG) (Brandwein et al., 2015; Castrén et al., 2003; Ethridge et al., 2016; Lepisto et al., 2005; Machado et al., 2013; Orekhova et al., 2007, 2008; Stroganova et al., 2007; Van der Molen et al., 2012a,b; van Diessen et al., 2014; Wang et al., 2013) or electromyography (EMG) and/or behavioral measures of pre-pulse inhibition and habituation of the startle reflex (Perry et al., 2007).

In the fields of ASD and FXS research, it is critical to develop translation-relevant outcome measures which bridge human and animal studies. Experimental approaches which measure sensory processing are emerging as powerful translational tools in this regard. Studies using EEG, magnetoencephalography (MEG) or startle/EMG point to analogous sensory processing deficits in humans and animal models (Castrén et al., 2003; Connolly et al., 2004; Ehrlichman et al., 2008; Ethridge et al., 2016; Harms et al., 2014; Lovelace et al., 2016; Maxwell et al., 2004; Nakamura et al., 2011; Siegel et al., 2003; Umbricht et al., 2004) and have facilitated examination of underlying mechanisms of sensory disorders in rodent models relevant to ASD/FXS. Furthermore, such studies take advantage of the properties of the neural circuitry underlying basic sensory processing, which is better characterized and may be more conserved across species than neural circuitry underlying complex social and communication behaviors.

In this review, we outline recent advances in understanding the sensory processing disruptions underpinning sensory features of ASD and FXS, focusing on the auditory sensory domain. Rather than exhaustively reviewing the literature as others have done (e.g. O'Connor, 2012; Orekhova and Stroganova, 2014), we highlight similarities and differences between auditory sensory processing deficits in ASD and FXS to highlight aspects of their shared and distinct pathophysiology. We then describe emerging evidence from rodent models which sheds light on the possible neurobiological underpinnings of sensory deficits in ASD, FXS and associated neurodevelopmental disorders.

2. Objective measurement of sensory processing

Auditory stimuli elicit stereotypical changes in electrical activity across the brain, which are reproducibly detected by EEG and can be accompanied by predictable behavioral responses. At a given location on the scalp (humans) or in the brain (rodents), changes in the electrical field represent the summation of extracellular currents generated by postsynaptic neurotransmission within neuronal networks (Creutzfeldt et al., 1966a,b), particularly those in closer proximity to the electrode. Measurement of these electrical field changes by EEG enables quantification of the amplitude, latency, frequency and power of neural oscillations, including those induced by sensory stimulation. An analogous technique, MEG, measures magnetic fields rather than electric fields in the brain and can also be used to quantify neural electrical activity (Cohen, 1972). Sound-evoked changes in electrical activity occur primarily in the brainstem/midbrain, thalamus, auditory cortex, amygdala, frontal cortex and temporal cortex, regions which are involved in processing of auditory sensory information.

Auditory processing advances through multiple stages, including pre-attentive stimulus recognition, sensory perception, active attentional shifting, salience detection and task-dependent activity (Picton and Hillyard, 1974; Picton et al., 1974). Below we describe a number of key experimental approaches which utilize EEG and/or behavioral measures in order to investigate auditory processing and sensory filtering in ASD.

2.1. Event-related potentials (ERPs)

Individual auditory stimuli each elicit a stereotypical pattern of voltage deflections in the EEG signal, which are known as event-related potentials (ERPs) and can be reliably quantified when responses to multiple auditory stimuli are averaged. For instance, the ERP following simple auditory stimuli, such as sounds with a particular intensity, pitch and duration, can be divided into discrete components. In humans, these components are termed the P50, P200, P300, N100 and N200 and consist of positive deflections at 50, 200 and 300 ms post-stimulus and negative deflections at 100 and 200 ms post-stimulus (Fig. 1; Duncan et al., 2009; Picton et al., 1974; Sutton et al., 1965). In rodents, analogous ERP components are seen, but are termed the P1, P2, P3, N1 and N2. They arise with shorter latencies, with P1, N1 and P2 components observed at approximately 20, 40 and 80 ms post-stimulus, respectively (Fig. 1; Broberg et al., 2010; Maxwell et al., 2004; Siegel et al., 2003; Umbricht et al., 2004; Witten et al., 2014). For consistency in this review, the rodent nomenclature will be used in both species. Individual ERP components have been linked to a number of aspects of sensory processing. The P1, N1 and P2 components are considered obligatory, in that they are evoked regardless of task or attentive state (Picton and Hillyard, 1974). The P1 is thought to reflect sensory registration and pre-attentive stimulus processing, the N1 cortical activation and sensory perception, and the P2 salience detection and stimulus evaluation. The P3, usually split into an earlier and more frontally located P3a and a later, more posterior (parietal) P3b component, is an index of novelty and attentional orienting elicited by infrequent or unpredictable elements introduced into otherwise predictable trains of stimuli (Polich, 2007; Polich and Criado, 2006; Sutton et al., 1965). Importantly, ERPs change across human and rodent postnatal development. In humans, there is evidence that P1 amplitude decreases and N1 and P2 amplitudes increases with age, although these changes differ depending on electrode location and vary between studies (Ponton et al., 2000; Wunderlich and Cone-Wesson, 2006; Wunderlich et al., 2006). In particular, children up to the age of 16 years display a prolonged, obligatory negative component which is less discernible in adulthood (Ponton et al., 2000; Sussman et al., 2008; Wunderlich et al., 2006). Latencies also change across development, with P1 and N1 latencies decreasing until adulthood (Ponton et al., 2000). In rodents, the opposite developmental patterns in ERP amplitude have been reported, with higher P1 amplitude and lower N1 and P2 amplitude in juvenile mice (7 weeks old) relative to adults (12 weeks; Featherstone et al., 2014; Nagy et al., 2015).

2.2. P1 (P50) suppression

Auditory stimuli not only induce ERPs and changes in neural oscillations, but also trigger the engagement of filtering mechanisms that modify responses to subsequent stimuli. At a neural level, this ‘gating’ phenomenon primarily involves the subconscious dampening of P1 responses to a second stimulus which occurs 0.5 s after the initial stimulus (Nagamoto et al.,

1991; Oranje et al., 2006). Abnormal P1 suppression involves a failure to diminish the P1 ERP response to the second click in a paired-click experimental paradigm (Freedman et al., 1983).

2.3. Acoustic startle and pre-pulse inhibition of startle (PPI)

A useful measure of general sensitivity to sensory auditory stimuli is the magnitude of the startle response to an acoustic stimulus (Braff et al., 1992; Swerdlow et al., 1994). This startle response can also be used to assess sensory filtering and sensorimotor gating. In a behavioral test called pre-pulse inhibition of startle (PPI), a loud tone or noise (around 115 dB) is presented either alone or preceded by a quieter tone/noise of approximately 72–85 dB, 30–500 ms beforehand. Maximum PPI is generally occurring at around 120 ms in humans (Braff et al., 1992; Graham, 1975), and at around 50 ms in rats. The extent of the acoustic startle response (ASR) is measured either by EMG measurement of eye muscle contraction (m. orbicularis oculi) in humans, or in rodents by the whole body twitch, sensed by a motion sensitive platform (Valsamis and Schmid, 2011). Humans or animals with normal PPI display strongly attenuated startle responses (by up to 70–90%) to the loud acoustic stimulus if it is preceded by the quieter pre-pulse stimulus, whereas individuals with diminished sensorimotor gating display less attenuation of startle responses by the pre-pulse (Braff et al., 1992; Swerdlow et al., 1994). The neural circuitry mediating acoustic startle responses is well-described and seems to be highly conserved (Schmid et al., 2014; Swerdlow et al., 1999). Secondary auditory neurons in the cochlear nucleus (cochlear root in mice and rats) innervate giant neurons in the caudal pontine reticular formation that directly activate cranial and spinal motorneurons (Koch, 1999; Nodal and Lopez, 2003; Swerdlow et al., 1999). PPI is thought to be mediated by a feed-forward inhibitory loop from the cochlear nucleus to the inferior and superior colliculi and the pedunculopontine tegmental nucleus, which in turn sends descending fibers to the startle mediating neurons in the reticular formation (Fendt et al., 2001; Gomez-Nieto et al., 2014; Swerdlow and Geyer, 1993; Yeomans et al., 2006).

2.4. Habituation, sensitization and refractory processes

Trains of stimuli induce additional changes in EEG and behav-ior, which either reflect refractory processes or the processes of habituation and sensitization. An example of refractory processes is the dampening of the N1 amplitude, following repeated high frequency stimulation: it may take up to 10 s for the N1 amplitude to fully recover after initial stimulation (Budd et al., 1998; Davis et al., 1966; Oranje et al., 2006). Habituation is the exponential decrement of a response to an initially novel stimulus that is presented repeatedly over time at lower frequencies, and it is different from refractory processes. Sensitization describes the opposite, an increment in response to the same stimulus over time. Habituation and sensitization are thought to be independent processes, modulating the same behavioural response in opposite ways (Groves and Thompson, 1970; Rankin et al., 2009; Schmid et al., 2014). An overall sensitization is often found in the first 2–4 trials of a block of startle-eliciting stimuli, followed by a gradual decline in responses (habituation) to the remainder of presented trials (Aggernaes et al., 2010; Meincke et al., 2004). Habituation (short-term) is assumed to be caused by synaptic mechanisms intrinsic to sensory pathways (Davis et al., 1982; Leaton et al., 1985; Simons-Weidenmaier et al., 2006). Specifically,

short-term habituation of startle has been proposed to be caused by activity-induced synaptic depression at the sensorimotor synapses in the pontine reticular formation, mediated by the activation of voltage- and calcium dependent large conductance potassium channels, called Maxi K, KCa1.1, or BK channels (Simons-Weidenmaier et al., 2006; Typlt et al., 2013b; Weber et al., 2002). Sensitization and long-term habituation are caused through an extrinsic modulation of the startle pathway by structures including the pedunculopontine tegmentum, the cerebellar vermis, the amygdala and the bed nucleus of the stria terminalis (Davis et al., 1997; Gonzalez-Lima et al., 1989; Koch, 1999; Leaton and Supple, 1986, 1991). The fact that these circuits are relatively well described, highly preserved, and that they can be studied in animal models, provides a unique opportunity for exploring potential mechanisms underlying sensory filtering disruptions in ASD and FXS, as well as for identifying potential drug targets to enhance sensory filtering.

2.5. Mismatch negativity (MMN)

Mismatch negativity (MMN) is another neural phenomenon reflecting underlying sensory filtering which is revealed by studying EEG responses to trains of auditory stimuli in humans (Näätänen et al., 2007) and rodents (Ehrlichman et al., 2008; Harms et al., 2014; Nakamura et al., 2011; Siegel et al., 2003; Witten et al., 2014). Unlike P1 suppression, PPI and habituation, which all dampen responses to less relevant stimuli, MMN involves the pre-attentive identification of more relevant stimuli among trains of less relevant ones. In the context of repeated stimuli of consistent pitch, duration and intensity, a deviant tone will elicit a negative deflection of the ERP at fronto-central and central electrodes (Näätänen et al., 2007), with a latency dependent on the paradigm used. Because it reflects the differences between evoked responses to two tones (standard and deviant), MMN is usually expressed as a difference wave.

2.6. Neural oscillations

Changes to the power and synchrony of neural oscillations also occur in response to auditory stimulation. These changes occur in the context of, and can be influenced by, the patterns of oscillations in resting state, where subjects are asked to think of nothing in particular. Both at rest and following stimulation, information about neural oscillations across a range of frequencies can be extracted from within the EEG signal using spectral decomposition approaches such as fast Fourier transformation or wavelet analysis (Fig. 1). Neural oscillations are important because, when divided into discrete frequency bands, they share physiological properties. Delta frequency oscillations (1–3 Hz) are particularly relevant to deep sleep, theta oscillations (4–7 Hz) to top-down cognitive control/memory, beta oscillations (13–30 Hz) to task engagement/motor behavior and gamma oscillations (30–80 Hz) to sensory and cognitive inhibition. In addition, changes in phase synchronization of the alpha frequency band (8–12 Hz) are thought to generate some components of the ERP, such as P1 and N2 (Gruber et al., 2005). Neural oscillations in rodents change across postnatal development, with increases in baseline power (Featherstone et al., 2014) and induced power (time-locked but not phase-locked to stimulus; Nagy et al., 2015) occurring during adolescence.

3. Sensory processing in individuals with ASD and FXS

3.1. ERPs

Abnormal auditory ERPs, consistent with impaired sensory processing, have been revealed by EEG in individuals with ASD. Decreased amplitude of the P1 peak at fronto-central electrodes has been described using both a classical P1 suppression paradigm in children aged 7–12 years with Asperger's syndrome (Madsen et al., 2015) and in children aged 7–12 years with ASD by presenting speech and non-speech sounds (Lepisto et al., 2005). This latter finding was replicated in a more recent study which reported decreased amplitude of a later component of the P1 in the central region in children aged 3–8 years with ASD (Stroganova et al., 2013). Increased variability of P1 amplitude and latency between trials may also occur in individuals with ASD (Milne, 2011). In a MEG study, increased latency of the M50 (equivalent to ERP P1) predicted language deficits in ASD (Oram Cardy et al., 2008). Decreased amplitude of the N1 component of the ERP has been observed in children with ASD aged 4–16 years (Bruneau et al., 1999; Gandal et al., 2010; Seri et al., 1999). Consistent with a role for early sensory processing abnormalities underpinning symptoms in ASD, a negative correlation between N1 amplitude (N1a at temporal electrodes and N1b at fronto-central electrodes) and autism symptom severity in children and adolescents 6–17 years has been reported (Brandwein et al., 2015). Increased N1 latency in ASD has been reported in some studies (Gage et al., 2003; Gandal et al., 2010; Korpilahti et al., 2007; Roberts et al., 2010) but not others (Bruneau et al., 1999; Ceponiene et al., 2003; Madsen et al., 2015). This may be explained in part by differences in mean age of subjects between studies, given that two studies using MEG have shown that normal age-related decreases in M100 between 8 and 16 years were absent in ASD individuals (Gage et al., 2003; Roberts et al., 2010). Such developmental differences may make detection of N1 latency differences in ASD more difficult in cohorts of younger children with a mean age <8 years (Bruneau et al., 1999; Ceponiene et al., 2003; Madsen et al., 2015) than older children with a mean age >9 years (Gage et al., 2003; Gandal et al., 2010; Korpilahti et al., 2007; Roberts et al., 2010). In addition to decreased amplitude of N1, decreased amplitude of N2 fronto-centrally for non-speech sounds has also been described (Lepisto et al., 2005). There is evidence that sensory processing deficits may be identifiable prior to ASD diagnosis. Increased P1 amplitude during standard repetitive speech stimuli in infants at high risk of ASD relative to children at low risk has been described (Seery et al., 2014), as has a failure of normal later-alization of ERPs during development in infants at high risk (Seery et al., 2013). These findings suggest a possible role for altered sensory processing as a risk factor for ASD and/or an early emerging symptom of the disorders.

Abnormalities of attentional orienting, indexed by P3 have also been investigated in ASD. The P3 consists of the P3a and P3b components, which are both elicited by infrequent or unpredictable elements introduced into otherwise predictable trains of stimuli. The P3a component occurs at 250–280 ms, and is present when infrequent or unpredictable shifts occur during a train of otherwise predictable stimuli regardless of where the participant is asked to direct his or her attention (Hruby and Marsalek, 2003; Squires et al., 1975). The P3a is therefore often described as a 'novelty detector' (Comerchero and Polich, 1999; Hruby and Marsalek, 2003). The P3b is also evoked by oddball tasks, and is observed at

250–500 ms (Polich, 2007). However, the amplitude of the P3b is dependent upon how improbable a stimulus is, with more improbable stimuli resulting in larger amplitude responses (Polich, 2007; Sutton et al., 1965). Both are elicited by infrequent or unpredictable elements introduced into otherwise predictable trains of stimuli (Hruby and Marsalek, 2003; Squires et al., 1975). Age dependent abnormalities of the P3a have been described in ASD, with increased P3a amplitude to pure tone deviants evident in childhood (less than 8 years of age) but decreased P3a amplitude evident in young adulthood in a small study (Ferri et al., 2003). Decreased P3a amplitude has been observed at younger ages (mean age 9 years) for vowel sound and speech-like frequency deviants in children with ASD and Asperger's syndrome (Ceponiene et al., 2003; Lepisto et al., 2005, 2006). Impairment of P3a in ASD is consistent with evidence of attentional deficits in ASD (for review see Orekhova and Stroganova, 2014), and suggests a common underpinning neurobiological mechanism.

Abnormal auditory ERPs have also been described in FXS. The published work is primarily on temporal and amplitude properties of the auditory ERPs (Knoth and Lippe, 2012; Rotschafer and Razak, 2014). A consistent observation across studies is that the N1 component has larger average amplitude and shows reduced habituation to repeated sounds in humans with FXS compared to control subjects (Castrén et al., 2003; Ethridge et al., 2016; Rojas et al., 2001; St Clair et al., 1987; Van der Molen et al., 2012a,b). A study using MEG also revealed enlargement and reduced latency of the N100 m (the MEG equivalent of the N1 in EEG) in adults with FXS (Rojas et al., 2001). Interestingly, the direction of N1 amplitude and latency changes in FXS is opposite that of ASD described above. Typically, FXS-related N1 enhancement is accompanied by P2 enhancement (Castrén et al., 2003; St Clair et al., 1987; Van der Molen et al., 2012a,b). Treatment with candidate pharmacotherapy minocycline can decrease N1 and P2 amplitudes in individuals with FXS (Schneider et al., 2013), suggesting that auditory ERP abnormalities can be used as outcome measures in drug treatment in human studies. Since both N1 and P2 components stem from temporal lobe activity, the altered N1 and P2 amplitudes are consistent with structural deficits in temporal lobe regions in humans with FXS, implicating this region in some of the behavioral abnormalities associated with FXS. These structural deficits include decreased size of superior temporal gyrus (Reiss et al., 1994), and white matter enlargement localized specifically to the temporal lobe (Hazlett et al., 2012). Additionally, fMRI research shows that the superior temporal gyrus, along with the medial frontal gyrus, middle temporal gyrus, cerebellum, and pons display higher levels of activation in individuals with FXS, consistent with the larger N1 component (Hall et al., 2009). Enhancement of the P2 component also suggests abnormal activation of the mesencephalic reticular activating system. Structures linked to P2 generation are also responsible for early auditory processing. Alteration of P2-associated structures may create an incorrect memory trace of the target stimulus, which may decrease performance on stimulus detection tasks (Näätänen et al., 2011, 2007).

The amplitude of the P3 component is also consistently reduced in humans with FXS (St Clair et al., 1987; Van der Molen et al., 2012a,b). Specifically, Van der Molen et al. (2012b,a) revealed reduced P3a and P3b components in individuals with FXS. Decreased P3b amplitude, specifically, may reflect a failure to identify a stimulus as improbable (Sutton et al., 1965), possibly resulting from improper stimulus representation at lower levels of processing, or from short term memory impairments (Polich, 2007).

In summary, various components of the auditory ERP are altered in FXS, with the N1/P2 changes predicting reduced habituation to a continuous acoustic environment. This may underlie the hypersensitivity phenotype observed behaviorally in humans with FXS. The changes in the longer latency components indicate improper memory trace formation that may result in reduced auditory change detection. Whether such deficits are present in early development has not been directly tested. However, if present, these deficits will leave an indelible mark on maturation of language and cognitive functions.

3.2. P1 (P50) suppression

Despite the phenotypic variation within the autistic spectrum, abnormal perception and processing of sensory information appears to be a shared phenomenon. Adequate processing of sounds and appropriate attention oriented towards them are considered prerequisites for accurate higher order processing. Similar to individuals with schizophrenia, it has been suggested that deficient inhibitory control of sensory stimuli in ASD may cause sensory overload and disruption of higher order processing, leading to avoidance of external stimulation altogether (Kootz et al., 1982). P1 suppression is a valuable index of inhibitory control of sensory stimuli, yet in ASD, research on P1 suppression has been sparse. There is some evidence for reduced P1 suppression in very young (3–8 years) autistic children with intellectual disability (IQ < 72), but this seemed to improve with age (Orekhova et al., 2008). Studies on older ASD subjects without intellectual disability showed comparable P1 suppression with typically developing children (Kemner et al., 2002), similar to that observed in the PDD-NOS subgroup Multiple Complex Developmental Disorder (MCDD) (Oranje et al., 2013b). Neither were P1 suppression deficits found in a study on adult males with ASD (Magnee et al., 2009). Healthy P1 suppression was also found in two recent studies on 8–12 year old children with ASD (Madsen et al., 2015), although a subpopulation of these children (those with Asperger's syndrome) showed attenuated P1 amplitude (Madsen et al., 2015). In summary, there is currently not much evidence for a P1 suppression deficit in autism, although on amplitude level the P1 ERP appears smaller in children with Asperger's syndrome. Future studies should include larger sample sizes not only in order to increase power, but also to allow grouping based on sub-diagnoses. Although inhibitory control of auditory sensory processing is also of interest in FXS, P1 suppression has not been investigated in FXS to our knowledge.

3.3. Acoustic startle and PPI

Acoustic startle reactivity has been used in ASD and FXS research as an objective measure of sensitivity to auditory stimulation. Increased startle magnitude in ASD, indicating higher auditory sensitivity, has been reported in both adults (Kohl et al., 2014) and children (Chamberlain et al., 2013; Takahashi et al., 2016). Other studies, however, have not found a general increase of startle magnitude in subjects with autism (Bernier et al., 2005; McAlonan et al., 2002; Salmond et al., 2003; Sterling et al., 2013; Yuhas et al., 2011). Because startle reactivity in individuals with ASD may be influenced by their level of functioning, these divergent results may have occurred in part due to differences in the severity and/or range of ASD symptoms in different cohorts. In a study which took into account ASD symptom severity, increased startle magnitude was only seen in higher functioning individuals (Kohl et al., 2014). Choice of auditory stimulus in the experimental

paradigms used may also have influenced the ability of some studies to detect startle abnormalities, since it has been shown that adult ASD subjects exhibit increased startle responses to pleasant stimuli, but not to neutral or unpleasant stimuli (Dichter et al., 2010; Wilbarger et al., 2009). Alongside possible increases in startle magnitude, increases in startle latency have also been reported in ASD (Ornitz et al., 1993; Takahashi et al., 2016; Yuhas et al., 2011). Like startle mag nitude, startle latency may be influenced by the severity of ASD symptoms. Whereas high-functioning individuals with ASD may display greater startle magnitude, they have been reported to display no change in startle latency (Bernier et al., 2005). Normal startle magnitude and latency have been reported in FXS (Frankland et al., 2004; Yuhas et al., 2011). Overall, although these studies of acoustic startle in ASD are consistent with increased sensitivity to auditory stimulation and altered sensory processing, further work is required to clarify the influence of stimulus valence and other experimental parameters on startle measurements. A greater understanding of whether startle reactivity correlates with specific ASD symptom profiles will also shed light on the translational and diagnostic utility of these measures.

PPI is an additional startle measure which has been investigated in ASD and FXS and takes advantage of the acoustic startle response to quantify sensorimotor gating. Reports on disruptions of PPI in ASD and FXS have not been consistent to date. For ASD, many studies on both adults as well as children with autism found no change in PPI (Kohl et al., 2014; Oranje et al., 2013b; Ornitz et al., 1993; Takahashi et al., 2016; Yuhas et al., 2011), while others report reduced PPI at least in adults (McAlonan et al., 2002; Perry et al., 2007). One study found slightly higher PPI levels at 76 dB pre-pulses in 8–12 year old children with autism (Madsen et al., 2014). Although it is possible that experimental variability or cohort heterogeneity is preventing reliable detection of subtle PPI deficits in ASD, it is currently not possible to conclude that altered PPI is a robust feature of ASD.

In contrast, individuals with FXS have robustly disrupted PPI compared to normal controls and individuals with ASD only (Frankland et al., 2004; Yuhas et al., 2011). Interestingly, although PPI deficits have been identified in FXS subjects regardless of their comorbid ASD diagnosis, they have also been correlated with the severity of autistic traits (Frankland et al., 2004), repetitive behavior (Perry et al., 2007) and several subscales of Social Responsiveness Scale and the Strength and Difficulties Questionnaire (Takahashi et al., 2016). This suggests that the PPI deficits in FXS reflect pathological sensory processing which also underpins the emergence of autism-related phenotypes in FXS. It also suggests that, although abnormal PPI has not been conclusively demonstrated in ASD, it may still be an informative indicator of abnormal sensorimotor gating in ASD and related disorders.

3.4. Habituation

Baseline startle reactivity is greatly influenced by short-term and long-term habituation (Valsamis and Schmid, 2011), which occurs independently of PPI and has been investigated in ASD, but not (to our knowledge) in FXS. Habituation is a form of sensory filtering and there is evidence that short-term habituation is slower at least in subpopulations of autistic individuals (Ornitz et al., 1993; Perry et al., 2007). Other studies which did not find differences in short-term habituation levels in ASD (Kohl et al., 2014; McAlonan et al.,

2002; Takahashi et al., 2016) may not have been well equipped to reveal any differences in the time scale of habituation, since blocks of responses before and after PPI testing were compared. Both short-term and long-term habituation deserve further investigation in children and adults with ASD and FXS.

3.5. MMN

MMN and other changes elicited by deviant auditory stimuli have also been investigated in ASD and FXS, in order to assess the integrity of pre-attentive auditory change detection mechanisms. Reports on MMN in ASD are highly inconsistent. Some studies report larger MMN amplitude in children with ASD (Ferri et al., 2003; Kujala, 2007; Lepisto et al., 2005, 2006), whereas others report smaller (Abdeltawwab and Baz, 2015; Ludlow et al., 2014) or equal amplitudes compared to typically developing children (Dunn et al., 2008; Jansson-Verkasalo et al., 2003; Roberts et al., 2011; Seri et al., 1999; Weismuller et al., 2015). Given the scope of this review, only MMN amplitude data are considered here. For information on MMN latency we refer the reader to other recent reviews (Kujala, 2007; Näätänen et al., 2011; Orekhova and Stroganova, 2014; Seri et al., 2007).

One likely contributor to disparities in the MMN studies described above is experimental differences between MMN paradigms, particularly at the level of the auditory stimuli used. Therefore, when considering here whether conclusions can be drawn from the MMN literature to date, we have subdivided MMN studies based on a) whether auditory stimuli consisted of pure tones (i.e. non speech-like) or more complicated, speech-like stimuli, and b) whether frequency or duration deviants were used.

In pure tone MMN paradigms, children with ASD have been reported to show either less (Abdeltawwab and Baz, 2015; Dunn et al., 2008), more (Ferri et al., 2003) or normal MMN to frequency deviants (Jansson-Verkasalo et al., 2003; Weismuller et al., 2015). Attention may impact consistency of findings with pure tone frequency deviants, given that one study reported reduced MMN amplitude to changes in frequency of pure tones in children with ASD in unattended conditions, but equal amplitudes in attended conditions (Dunn et al., 2008). Although the above mentioned studies were typically conducted in unattended conditions, the nature of the distractor stimulus differed substantially between studies (e.g. animated silent movie, picture book, etc.), and may have had different salience for individuals of different ages within each study. Electrode placement may also play a role, given that in some work, MMN amplitude deficits to pure tone frequency deviants could only be detected in children with ASD when the topography of the electrodes was taken into account, since maximal MMN amplitude was observed at the frontal Fz electrode in controls and more posterior C3/4 electrodes in individuals with ASD (Gomot et al., 2002). While some studies only record at Fz (Abdeltawwab and Baz, 2015; Seri et al., 1999), others use the International 10–20 System to record at multiple sites (Weismuller et al., 2015). Inconsistent results found with pure tone paradigms may also have been caused by differences in composition of ASD cohorts. Overall, the data seems to suggest a decrease in MMN to pure tone deviants, although further work is required to confirm this effect.

In MMN paradigms employing speech-like stimuli, a disparate picture is also seen. There is some evidence indicating that MMN to complex speech-like deviants or vowel/word change

is reduced in children with ASD compared to typically developing children (Kuhl et al., 2005; Kujala et al., 2010; Ludlow et al., 2014). However, other studies have not reported such diagnostic differences (Ceponiene et al., 2003; Kasai et al., 2005; Oram Cardy et al., 2005; Weismuller et al., 2015), or have reported enhanced MMN amplitude to frequency deviants or affective prosody in ASD or Asperger's syndrome compared to typically developing children (Korpilahti et al., 2007; Lepisto et al., 2005, 2006). In the studies of Lepisto and colleagues, increased MMN in ASD and Asperger's syndrome was not found at the usual frontal electrodes (Fz) but rather only at parietal electrodes, possibly reflecting the MMN in primary auditory cortex and reinforcing that differences in the locations of recording electrodes may impact the ability to detect MMN abnormalities in ASD. In circumstances where there may be increased MMN to frequency deviants in ASD, this may not be accompanied by concordant increases for duration deviants since studies reporting increased MMN to frequency deviants in ASD also report normal (Lepisto et al., 2005) or decreased (Lepisto et al., 2006) MMN to duration deviants.

Despite the disparity of MMN findings in both pure tone and speech-like stimulus paradigms, there are two areas in which a more consistent picture is emerging. Firstly, studies employing a range of paradigms have reported that normal lateralization of MMN is diminished or absent in ASD subjects compared to healthy controls (Jansson-Verkasalo et al., 2003; Korpilahti et al., 2007; Kuhl et al., 2005; Lepisto et al., 2006; Weismuller et al., 2015). Unfortunately, due to the placement of electrodes, many studies are not designed to compare MMN in both hemispheres. Secondly, multiple studies have reported a relationship between MMN and measures of ASD symptom severity (such as sensory profiles, auditory preference etc.). These studies, which found decreased MMN in ASD, reported that greater MMN deficits were associated with increased sensory sensitivity (Ludlow et al., 2014), decreased auditory preference for speech (Kuhl et al., 2005) and increased CARS score (Abdeltawwab and Baz, 2015). These observations suggest that, in some cohorts of individuals with ASD, impairment of sensory filtering and auditory change detection are associated with, and may underlie, sensory hypersensitivity and other autism-related phenotypes.

In summary, the results of studies on MMN in ASD are inconsistent, although there seems to be some evidence for deficient MMN amplitudes in children with ASD and FXS. It is challenging to determine which factors contribute most to this variability, given that studies differ in the nature of auditory stimulus and deviant, EEG recording locations, ages of subjects and severity of subjects' ASD symptoms and comorbidities. Future studies should include larger sample sizes, so that comorbidity and levels of anxiety can be taken into account and the ASD cohort split in meaningful (DSM-V based) subcategories. Furthermore, studies should use standardized paradigms for measurements and data analyses, or at least report on a standard set of electrodes (in combination with interesting results from other electrodes), in order to facilitate comparisons of results across studies.

In FXS, MMN and other changes elicited by deviant auditory stimuli have also been investigated. In addition to the abnormally high amplitude, an inability of the N1 amplitude to distinguish between a standard tone of high probability of occurrence and an 'oddball' tone of low probability of occurrence has been described in FXS (Van der Molen et al.,

2012a,b). In control subjects, the average N1 amplitude was smaller for the standard tone compared to the oddball tone, while in individuals with FXS, the standard and oddball tones elicited similar N1 responses (Van der Molen et al., 2012a,b). Enlargement of the N2b wave (Van der Molen et al., 2012a,b) and increased N2 latency (St Clair et al., 1987; Van der Molen et al., 2012a) have also been seen in individuals with FXS. However, despite a general increase in N2 amplitude, decreased MMN to pure tone frequency deviants has been reported in individuals with FXS (Van der Molen et al., 2012b). As was observed in ASD (Gomot et al., 2002), the maximal MMN amplitude was identified at different electrodes in FXS and control individuals (Van der Molen et al., 2012b). Given the scarcity of studies of MMN in FXS, further work is required to confirm increased MMN and altered sensory filtering in FXS.

3.6. Baseline and evoked changes in neural oscillations

Abnormal ‘baseline’ neural oscillations have been reported in ASD. In the resting state, increased power of low frequency (delta and theta) and high frequency (beta, gamma) oscillations, alongside decreased power of mid-range (alpha) oscillations, have been described in children and adults with ASD (Machado et al., 2013; Orekhova et al., 2007, 2008; van Diessen et al., 2014), (reviewed in Wang et al., 2013). In children aged 3–8 years with ASD, increased baseline gamma was negatively correlated with P1 suppression, such that increased baseline gamma was associated with greater impairment of P1 suppression (Orekhova et al., 2008).

Altered neural oscillatory responses to sensory stimulation have also been reported in ASD. Increased gamma power and decreased phase-locking of gamma oscillations in response to auditory stimuli have been described in individuals with ASD and/or their parents, as detected by MEG (McFadden et al., 2012; Rojas et al., 2011, 2008). Abnormal synchrony of oscillations across the theta and gamma bands in response to speech in ASD has also been described (Jochaut et al., 2015). The observed failure of theta activity in auditory cortex to downregulate gamma oscillations in response to speech was correlated with verbal impairment and general autism symptoms (Jochaut et al., 2015). These few above-mentioned studies are consistent with other studies using visual cues (such as faces) that have also revealed abnormal evoked oscillations in ASD, particularly in the gamma frequency range (Grice et al., 2001; Keehn et al., 2015; Wright et al., 2012). Overall, studies of baseline and evoked neural oscillations in ASD support a role for impaired resting state and auditory-evoked cortical activity in sensory processing deficits in ASD.

Although patterns of neural oscillations have not been extensively investigated In FXS, two studies have indicated that resting (baseline) power of neural oscillations, and underlying functional connectivity, are impaired in FXS. As observed in ASD, increased baseline theta (4–8 Hz) power occur has been described in FXS (Van der Molen and Van der Molen, 2013). Also consistent with ASD, decreased alpha power (in this case, in the upper alpha 10–12 Hz range) is also seen in individuals with FXS (Van der Molen and Van der Molen, 2013). In that study, oscillations in other frequency bands (beta 13–30 Hz and gamma 30–80 Hz) were not investigated. Finally, functional connectivity computed from the resting EEG phase lag index is reportedly altered in FXS, with increased resting theta functional connectivity and

decreased resting alpha and beta functional connectivity mirroring diagnostic differences in baseline neural oscillations (van der Molen et al., 2014). These abnormalities in baseline neural oscillations suggests that, as in ASD, impaired resting state cortical activity may play a role in altered sensory processing and cognitive function in FXS.

A summary of auditory sensory processing abnormalities in ASD and FXS is provided in Table 1.

4. Sensory processing in rodent models relevant to FXS and ASD

4.1. Animal models relevant to FXS

The fragile X mental retardation 1 (*Fmr1*) knock out (KO) mouse is a pre-clinical animal model to study the pathophysiology underlying FXS with well-characterized construct and face validity (Bakker et al., 1994). Fmr1 KO mice lack the Fragile X Mental Retardation Protein (FMRP) and show several FXS-and ASD-like symptoms (Bernardet and Crusio, 2006), including social impairments (Spencer et al., 2005), repetitive behaviors (Crawley, 2004, 2007), heightened anxiety (Bilousova et al., 2009), hyperactivity that may be related to increased arousal in a novel environment (Kramvis et al., 2013) and altered ultrasonic vocalization communication by both pups and adults (Rotschafer et al., 2012; Roy et al., 2012). Physical alterations seen in humans such as macro-orchidism are also seen in the Fmr1 KO mouse (Lachiewicz and Dawson, 1994; Sidhu et al., 2014). One caveat to consider in examining predictive validity in the mouse model include the fact that in the Fmr1 KO mouse, the protein FMRP is virtually absent, whereas in humans with FXS, the number of CGG repeats influences FMRP levels and the range of resulting deficits. It is also important to note that there are mouse strain specific differences that interfere with different measures (Bernardet and Crusio, 2006). Nevertheless, the Fmr1 KO mouse recapitulates several FXS-like symptoms and is a commonly used pre-clinical model (Kooy et al., 1996). Most encouragingly, Fmr1 KO mice also exhibit sensory system deficits. These deficits have been measured in terms of increased susceptibility to audiogenic seizures, increased response of sensory cortex to stimuli (Rotschafer and Razak, 2014; Zhang et al., 2014), increased UP states in sensory cortex (Hays et al., 2011), increased spontaneous and correlated activity in sensory cortex (Goncalves et al., 2013) and reduced habituation of sensory stimulus evoked responses (Lovelace et al., 2016). Some of these deficits may arise due to abnormal critical period plasticity during development (Contractor et al., 2015; Kim et al., 2013).

Prominent deficits appear consistently in auditory sensitivity. FMRP is expressed across multiple levels of the auditory neuraxis (Wang et al., 2014). Genetic removal of FMRP in the mouse model results in increased propensity for audiogenic seizures, suggesting hypersensitive auditory responses. In Fmr1 KO mice, auditory stimuli with sound levels >100 dB SPL can cause a period of wild running, tonic/clonic seizing, and death (Chen and Toth, 2001; Musumeci et al., 2000, 2007). Reintroduction of FMRP to Fmr1 KO mice significantly reduced audiogenic seizure susceptibility (Musumeci et al., 2007). In terms of acoustic startle responses and their modulations, Fmr1 KO mice seemed to have an opposite phenotype to what was found in human studies: they display lower startle responses, and higher PPI (Chen and Toth, 2001; Frankland et al., 2004; Olmos-Serrano et al., 2011; Yun et al., 2006), although one group found PPI to be normal in these mice PPI (Uutela et al.,

2012). However, Nielsen et al. (2002) showed that startle responses were decreased only at higher amplitude stimuli, and actually increased at lower startle stimulus amplitudes, resembling individuals with FXS in their increased sensitivity to low intensity auditory stimuli. It would be interesting to see if PPI in Fmr1 KO mice also depends on stimuli intensity and is increased at lower prepulse/pulse combinations.

Recent studies have revealed an exciting potential connection between the molecular alterations in FXS and startle habituation mechanisms: it has been shown that FMRP directly interacts with synaptic BK channels, which in turn have been shown to be crucial for short-term habituation (Deng et al., 2013; Hebert et al., 2014; Typlt et al., 2013b; Zhang et al., 2014). Unfortunately, startle habituation is not well studied in humans with FXS or Fmr1 ko mice, however, the allosteric BK channel activator BMS-204352 was shown to reverse behavioural and cellular FXS symptoms in Fmr1 ko mice (Hebert et al., 2014), highlighting the potential of studying sensory filtering mechanisms in animal models for developing pharmaceutical treatments. More potent and specific BK channels modulators are currently developed and in clinical trials (mostly for stroke and/or epilepsy treatment), however, the abundant BK channel expression in the periphery, e.g. in the myocardium, vasculature, and bladder, pose a major challenge.

To address the mechanisms that may underlie the differences in auditory processing in FXS, (Rotschafer and Razak, 2014) performed in vivo extracellular single neuron recordings from the auditory cortex of the Fmr1 ko and wildtype (WT) mice. Fmr1 ko mouse cortex showed four main processing deficits in the primary auditory cortex (A1) at the single neuron level: (1) Hyper-excitability: cortical neurons in KO mice respond with more action potentials to tones than WT neurons. The increased response was due to prolonged spiking indicating that the KO neurons failed to shut down their responses after sound offset. This may underlie the hyper-excitability phenotype in both humans with FXS and the mouse model (2) Increased variability: the first spike latency in response to tones in KO mice neurons was more variable indicating that the neurons were not providing consistent information for repetitions of the same sound. (3) Broader receptive fields: the excitatory frequency tuning curves are broader in the KO mice neurons. This indicates that for a given tone, more neurons will be activated. This may explain the larger amplitude and more widespread activation of the auditory cortex in FXS. (4) Reduced spectrotemporal selectivity: reduction in selectivity for the rate of frequency modulated (FM) sweeps. This was because the KO neurons responded better to much shorter duration sounds and faster changes in frequency that WT neurons. The robust responses to sounds as short as <3 ms in KO neurons is typically not seen in WT neurons and indicates that the KO neurons have a different temporal integration window and are easier to stimulate than WT neurons.

The *in vivo* single neuron electrophysiology data suggest deficits in spectral and temporal processing in auditory cortex of KO mice that may relate to auditory deficits in humans with FXS. Preliminary data based on auditory ERPs from the Fmr1 KO mouse cortex suggests a more directly translation relevant phenotype in the mouse (Lovelace et al., 2016). Auditory ERPs were measured using electrodes placed between 200 and 400 μm deep in the primary auditory cortex of anesthetized Fmr1 KO and WT mice. Repeated presentation of a sound stimulus (tones or noise) at various repetition rates (0.25–5 Hz) showed a robust reduction in

habituation of the N1 component for repetition rates faster than 1 Hz in the Fmr1 KO mice. The similar habituation deficit in auditory ERP habituation in humans and mice provides a useful translation relevant functional marker to include in drug development for FXS. The deficit in early sensory processing will also allow an examination of circuit and cellular deficits (Gibson et al., 2008; Hays et al., 2011; Selby et al., 2007) that may be more tractable than complex social behaviors and importantly conserved across species.

4.2. Animal models of possible etiologic factors in idiopathic ASD

There is a huge range of transgenic mouse lines which model possible etiologic factors in ASD and show analogies to the diagnostic symptoms of autism, including low social interactions, reduced vocalizations in social settings, and high levels of repetitive self-grooming. Table 2 lists relevant rodent strains and their respective ERP, MMN, startle reactivity, PPI and neural oscillation abnormalities. Most of them show distinct alterations in startle reactivity and/or PPI, which has been the focus of sensory processing characterization in rodent models of ASD even though findings in humans with ASD are not consistent. In contrast, ERPs, MMN, habituation and neural oscillations have been less commonly assessed even though abnormalities of these measures in ASD are more replicable. Some strains have been studied further for sensory processing abnormalities. For example, contactin associated like protein 2 (Cntnap2) was first associated with Specific Language Impairment (SLI) and has been linked to ASD. Cntnap2 homozygous null mice have shown distinct alterations in auditory processing, i.e. in silent gap detection and pitch discrimination (Rendall et al., 2015; Truong et al., 2015), and increased PPI (Brunner et al., 2015). Of special interest is also the BK-channel knock-out mouse that shows disruptions in short-term habituation of startle, along with repetitive self-grooming, mild PPI deficits, and specific cognitive deficits (Typlt et al., 2013a,b). As mentioned above, BK channels are crucial for short-term habituation, Fragile x mental retardation protein directly interacts with synaptic BK channels (Deng et al., 2013; Hebert et al., 2014; Typlt et al., 2013b; Zhang et al., 2014).

Apart from genetic factors, maternal infections and exposure to valproate (VPA) during pregnancy have been shown to greatly increase the risk for a child to develop autism. This has led to the establishment of respective animal models. One of the best established ASD models are intraperitoneal injections of 600 mg VPA at gestation day 12.5 in rats which causes cardinal symptoms of ASD in the offspring (reviewed by Roullet et al., 2013). Prenatal VPA treatment increases ERP N1 latency, decreases evoked gamma power and decreases gamma phase locking (Gandal et al., 2010). It also reduces PPI in young rodents, and to a lesser extent in adult rodents, while startle response amplitudes seem to be unchanged (Schneider and Przewlocki, 2005; Schneider et al., 2006). Postnatal treatment with 150 mg/kg VPA for six days reduces startle responses and impairs PPI in adult rats as well (Reynolds et al., 2012). Interestingly, offspring of a male rat of advanced paternal age (another risk factor for ASD identified in humans; Sandin et al., 2015) has also shown to reduce startle reactivity and impair PPI (Milekic et al., 2015).

Maternal infections during pregnancy can be mimicked by injections of Lipopolysaccharides (LPS) or Polyinosinic:polycytidylic acid (poly-IC). Prenatal LPS seems to increase startle

reactivity at least in male offspring (Foley et al., 2015) and induces PPI deficits (Fortier et al., 2007). Prenatal immune challenge by poly-IC leads to either less startle reactivity in rats (Vorhees et al., 2015), or unchanged startle responses (Howland et al., 2012; Meyer et al., 2008), but consistent with VPA models disrupts PPI in the offspring (Howland et al., 2012; Meyer et al., 2008; Vorhees et al., 2015). Likewise, influenza virus injection at gestational day 9.5 in mice leads to PPI deficits in adolescence (Shi et al., 2003).

In conclusion, a range of different rodent models show some or all of the cardinal symptoms of ASD, have face and/or construct validity, and show changes in startle reactivity and/or PPI, indicating that sensory processing and sensory filtering is affected in these models. Changes in startle responsiveness, habituation, and PPI depend greatly on the specific parameters used, such as stimulus intensities and temporal properties. Unfortunately, parameters vary substantially between studies. This might explain some of the variability in startle modulations between different animal models. Like in human studies, some variability might be inherent, due to the fact that different perturbations all lead to autistic symptoms, while having different (even opposite) effects on sensory processing and sensory filtering. Nevertheless, these animal models provide the unique opportunity to study cellular and molecular mechanisms underlying the emergence of ASD and FXS symptoms.

4.3. Animal models of circuit changes that recapitulate ASD phenotypes

Abnormal ERPs and neural oscillations, akin to deficits in ASD, are evident in a number of rodent models of disrupted excitatory/inhibitory balance. Three such models, of constitutive pan NMDA receptor hypofunction (Gandal et al., 2012a,b), cell-type specific NMDA receptor ablation (Saunders et al., 2013) and transient NMDA receptor blockade (Saunders et al., 2012), have shed light on mechanisms which may underlie the emergence of electrophysiological and sensory processing deficits in ASD (Table 3).

Mice which have widespread, constitutively decreased expression of the obligatory GluN1 subunit of the NMDA receptor ($GluN1^{neo-/-}$) display disrupted sensory processing and other ASD relevant phenotypes. In the hippocampus, $GluN1^{neo-/-}$ mice exhibit delayed N1 latency, increased baseline gamma power, decreased auditory evoked gamma power and decreased evoked gamma phase synchrony/inter-trial coherence (ITC) (Gandal et al., 2012a,b; Halene et al., 2009), reminiscent of ASD (Bruneau et al., 1999; Gage et al., 2003; Gandal et al., 2010; Machado et al., 2013; Orekhova et al., 2007, 2008; van Diessen et al., 2014). ERP and gamma frequency abnormalities were accompanied by decreased PPI, decreased premating ultrasonic vocalizations, diminished social preference, decreased anxiety-like behavior and stereotyped behaviors (Gandal et al., 2012a,b; Halene et al., 2009). A number of other impairments in $GluN1^{neo-/-}$ mice point to generalized neuronal hyper-excitability due to dysfunction of fast spiking par-valbumin (PV)-positive interneurons as the central pathology in these mice, consistent with a number of other ASD mouse models including the neuroligin-3 R451C, PDGFR-β KO and prenatal VPA models which also show PV interneuron pathology (Gogolla et al., 2009; Nakamura et al., 2015). This is also similar to the PV neuron dysfunction observed in the cortex of Fmr1 KO mice (Gibson et al., 2008; Hays et al., 2011). Impairments in the $GluN1^{neo-/-}$ mice included decreased protein expression of the GABA-A receptor and parvalbumin, and increased pyramidal neuron

intrinsic excitability (Gandal et al., 2012b). Abnormal PV protein expression has also been observed in ASD but in contrast to GluN1$^{neo-/-}$ mice, PV immunoreactivity was increased in postmortem ASD tissue (Lawrence et al., 2010). Interestingly, the constellation of EEG abnormalities and behavioral impairments were remediated by treatment with baclofen, a GABA-B agonist (Gandal et al., 2012b), lending preclinical support to a therapeutic approach trialed in ASD and highlighting the utility of EEG in rodent studies as a measure of treatment responsiveness.

Cell-type specific NMDA receptor ablation also results in ASD-relevant circuit changes and behavioral deficits (Carlén et al., 2012; Saunders et al., 2013), but to a lesser extent than the constitutive knockdown described above. Knockout of GluN1 selectively in PV-positive interneurons increased N1 latency in auditory cortex and deceased social preference (Billingslea et al., 2014; Saunders et al., 2013). Decreased premating ultrasonic vocalizations in PV-selective GluN1 KO mice were also described, but other behaviors such as spatial working memory were intact. Increased baseline gamma power and decreased light-evoked gamma power have also been also identified in PV-selective GluN1 KO mice using EEG (Billingslea et al., 2014) and also local field potential measurement and optogenetic stimulation (Carlén et al., 2012), but baseline gamma increases were less prominent when recorded in awake animals using EEG. These electrophysiological abnormalities were accompanied by impaired habituation and subtle spatial working memory deficits (Carlén et al., 2012). Consistent with these studies, and supporting the presence of an ASD-relevant phenotype in mice lacking the NMDA receptor in interneurons, mice expressing Cre recombinase under the Ppplr2 promoter (expressed predominantly in interneurons) displayed impaired neuronal synchrony (measured by single unit recordings), alongside decreased PPI and spatial working memory (Belforte et al., 2010). These findings further strengthen the validity of rodent models of NMDA receptor hypofunction, particularly in PV-positive interneurons, for investigation of sensory processing in ASD.

Finally, transient blockade of NMDA receptors can also mimic sensory processing deficits seen in ASD. Treatment of mice with NMDA receptor antagonist MK801 increases N1 ERP latency, disrupts PPI and baseline gamma power, but decreases evoked gamma power and phase synchrony (ITC) and (Bakshi and Geyer, 1998; Bast et al., 2000; Saunders et al., 2012), resulting in a phenotype similar to that seen in ASD (Gandal et al., 2010; McFadden et al., 2012; Orekhova et al., 2008; Rojas et al., 2011, 2008). Treatment with ketamine, an NMDA receptor antagonist which also acts at other sites, also increases baseline gamma power and decreases MMN (Ehrlichman et al., 2009; Ehrlichman et al., 2008; Lazarewicz et al., 2010; Long et al., 2015). However, it decreases rather than increases N1 latency (Connolly et al., 2004; Maxwell et al., 2006) and increases rather than decreases evoked gamma power (Lazarewicz et al., 2010). Interestingly, chronic ketamine exposure in juvenile mice rather than adults induces different deficits in ERPs and neural oscillations (Featherstone et al., 2014). Juvenile ketamine exposure (from post-natal days 28–42) does not increase baseline gamma oscillations over and above the normal developmental increase in gamma power, but results in the delayed emergence of decreased total event-related gamma power and decreased P20 amplitude (Featherstone et al., 2014). Broadly speaking, the deficits of baseline and auditory-evoked neural oscillations arising from pharmacologically-induced NMDA receptor hypofunction mirror deficits seen in

constitutively GluN1-underexpressing GluN1$^{neo-/-}$ mice (Gandal et al., 2012b), but likely depend on age of exposure and the pharmacological properties of the antagonist. Overall, these models suggest that transgenic rodents whose neurological and behavioral abnormalities recapitulate deficits in ASD may be useful tools in understanding underlying cellular and circuit pathologies in the disorders.

5. Key similarities and differences in sensory processing measures between ASD and FXS

As the most common known genetic cause of ASD, FXS can be used powerfully as a window into pathophysiological mechanisms in ASD. However, only one quarter and one third of individuals with FXS are also diagnosed with ASD (Bailey et al., 2008; Rogers et al., 2001), and individuals with FXS who do not have ASD display sensory processing abnormalities similar to, but not the same as, those seen in ASD. It follows, therefore, that some objective sensory processing measures which are similarly dysregulated in FXS and ASD may shed light on mechanisms underlying shared sensory processing deficits, while other measures which display different patterns of dysregulation may illuminate aspects of sensory processing which are distinct in the two disorders.

The sensory processing measures which appear to be most consistent between FXS and ASD are sensory filtering and attentional orienting measures, MMN and the P3a respectively. These measures are both evaluated in paradigms which feature rare, deviant stimuli and can be tailored to target filtering of speech or non-speech auditory stimuli. Although findings with MMN in ASD are variable, many studies have reported decreased MMN (Abdeltawwab and Baz, 2015; Dunn et al., 2008; Kuhl et al., 2005; Kujala et al., 2010; Lepisto et al., 2005, 2006; Ludlow et al., 2014), which is negatively correlated with symptom severity (Abdeltawwab and Baz, 2015; Kuhl et al., 2005; Ludlow et al., 2014). Decreased MMN is also reported in FXS (Van der Molen et al., 2012b). Similarly, a consistent picture of decreased P3a amplitude, particularly with speech-like stimuli in individuals greater than 10 years of age, has emerged (Ceponiene et al., 2003; Ferri et al., 2003; Lepisto et al., 2005, 2006), consistent with the decreased P3a amplitude observed in FXS (Van der Molen et al., 2012a,b). It is plausible that sensory filtering and attentional orienting mechanisms underlying MMN and the P3a represent points of convergence for sensory processing deficits in FXS and ASD. In contrast, ERP abnormalities such as N1 amplitude, N1 latency and N2 amplitude consistently display opposite patterns of dysregulation in FXS and ASX (Brandwein et al., 2015; Bruneau et al., 1999; Castrén et al., 2003; Gage et al., 2003; Gandal et al., 2010; Korpilahti et al., 2007; Lepisto et al., 2005; Roberts et al., 2010; Rojas et al., 2001; Seri et al., 1999; St Clair et al., 1987; Van der Molen et al., 2012a,b). As a result, it is possible that early auditory processing mechanisms supporting generation of early ERP components are dysregulated in different ways in FXS and ASD, resulting in divergent sensory processing abnormalities in some areas. It is important to note that more work needs to be done in FXS to examine spectral characteristics of EEGs to determine if similarities with ASD exist in these measurements.

One way in which future studies of FXS could further strengthen understanding of ASD would be for such studies to subgroup FXS individuals into those with and without ASD. Subgrouping of those with comorbid intellectual disability and those without would also be beneficial. Although challenging due to the low incidence of FXS, such an approach would enable disentangling of the mechanisms underlying the emergence of ASD phenotypes from those underlying other symptom features of FXS.

The models described above also have cross-diagnostic utility for understanding impairments of sensory processing. Although the main focus of this review is on autism and FSX, it is important to realize that many of the electrophysiological measures that are described in this review have also been implicated in schizophrenia. Similarities such as increased baseline gamma power, decreased evoked gamma power, decreased P1 suppression and decreased PPI (Braff et al., 1992; Freedman et al., 1996, 1983; Hanlon et al., 2005; Kwon et al., 1999; Spencer et al., 2003), as well as decreased MMN amplitude in both disorders (Atkinson et al., 2012; Baldeweg et al., 2002) have been reported in both ASD and schizophrenia. However, other studies indicate that there might be marked differences, such as that some studies found normal levels of both PPI and P1 suppression in children with autism (Kemner et al., 2002; Kohl et al., 2014; Madsen et al., 2015; Oranje et al., 2013b; Ornitz et al., 1993), while deficient levels are robustly found in schizophrenia (Aggernaes et al., 2010; Braff et al., 2001; Oranje et al., 2013a; Thibaut et al., 2015). There seems to be at least some overlap between schizophrenia and autism symptoms: in two Danish register based studies it was shown that, dependent on the specific form of autism, up to 30% of individuals with a childhood diagnose of autism develop a schizophrenia spectrum disorder later in life (Mouridsen et al., 2008a,b), while parental reports suggest that up to 60% of patients with schizophrenia have had a history with autistic symptoms (Unenge Hallerback et al., 2012).

6. Overlapping sensory processing deficits in ASD and schizophrenia

Although the main focus of this review is on autism and FSX, it is important to realize that most of the electrophysiological measures that are described in this review have also been implicated in schizophrenia. Similarities such as increased baseline gamma power, decreased evoked gamma power, decreased P1 suppression and decreased PPI (Braff et al., 1992; Freedman et al., 1996, 1983; Hanlon et al., 2005; Kwon et al., 1999; Spencer et al., 2003), as well as decreased MMN amplitude in both disorders (Atkinson et al., 2012; Baldeweg et al., 2002) have been reported in both ASD and schizophrenia. However, other studies indicate that there might be marked differences, such as that some studies found normal levels of both PPI and P1 suppression in children with autism (Kemner et al., 2002; Kemner et al., 1995; Kohl et al., 2014; Madsen et al., 2015; Oranje et al., 2013b; Ornitz et al., 1993), while deficient levels are robustly found in schizophrenia (Aggernaes et al., 2010; Braff et al., 2001; Oranje et al., 2013a; Thibaut et al., 2015). There seems to be at least some overlap between schizophrenia and autism symptoms: in two Danish register based studies it was shown that, dependent on the specific form of autism, up to 30% of individuals with a childhood diagnose of autism develop a schizophrenia spectrum disorder later in life (Mouridsen et al., 2008a,b), while parental reports suggest that up to 60% of patients with schizophrenia have had a history with autistic symptoms (Unenge Hallerback et al., 2012).

7. Concluding discussion

Sensory dysfunction, particularly in the auditory domain, is consistently seen in ASD and FXS. Basic sensory processing circuitry may be relatively more tractable compared to circuits involved in social communication and cognitive aspects of ASD. Circuitry involved in basic sensory processing may also be more conserved across humans and mice compared to circuits involved in cognitive and social communication. These observations suggest that sensory processing offers a unique opportunity to understand the patho-physiology of ASD/FXS at a circuit and cellular level. Future studies are required to elucidate the molecular mechanisms of altered auditory subcortical and cortical processing and how these differences correlate with auditory behaviors in ASD and FXS.

ASD and FXS are neurodevelopmental disorders, but little is known about how the auditory processing deficits develop, and how these deficits impact the further development of the brain. Therefore, additional behavioural and anatomical studies in humans and animals, as well as *in vivo* single neuron and ERP recordings in animals, are required. Such studies may identify correlations between developmental hyper-excitability, habituation deficits and responses to treatments, enabling identification of specific patient subgroups suited to specific therapeutic approaches. In rats and mice, it will be important to study how proteins implicated in ASD and FXS, such as CNTNAP2 and FMRP, contribute to the normal developmental maturation of neurons, auditory circuits, and e.g. ERP responses. Ultimately, studies of sensory processing in ASD and FXS may reveal mechanisms underlying developmental disruptions in ASD and FXS, offering hope for individually targeted, age-specific therapeutic approaches in the future.

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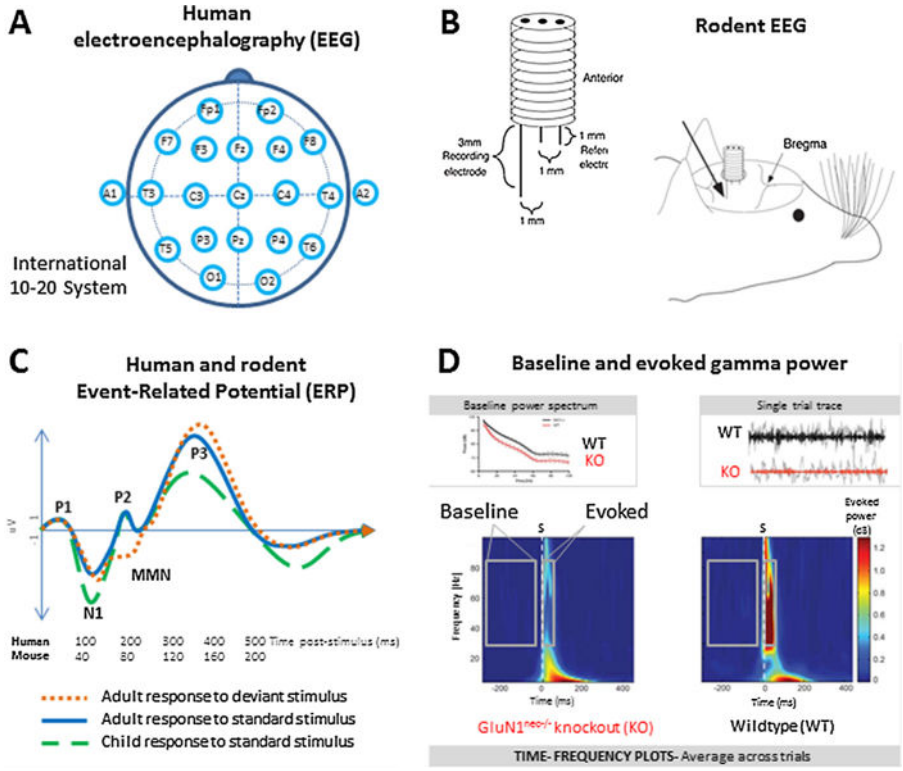

Fig. 1.

Schematic representation of human and rodent EEG electrode placement, ERPs and gamma oscillations.

A) Human scalp EEG array using the International 10–20 System for electrode placement; B) example of rodent EEG using implanted tripolar electrodes; C) schematic representation of stereotypical auditory-evoked ERP with characteristic positive and negative voltage deflections. ERP latencies and peaks can vary according to electrode placement, experimental paradigm and species; D) example of neural oscillations-gamma oscillations at baseline and following auditory stimulus, contrasting wildtype and GluN1 knockout mice. S – stimulus, KO – knockout, WT – wildtype. Panel B adapted from Connolly et al. (2003) with permission, panel C adapted from Gandal et al. (2012b) with permission.

Table 1

Comparison of sensory processing deficits in Autism Spectrum Disorder and Fragile X Syndrome, as measured by EEG, MEG and EMG. Refer to the text for discussion of possible reasons for divergent findings; *to our knowledge.

Objective measure of auditory sensory processing	Autism Spectrum Disorder	Fragile X syndrome
Event-related potentials		
P1 amplitude	Decreased P1 amplitude (Ceponiene et al., 2003; Lepisto et al., 2005; Stroganova et al., 2013); (Asperger's syndrome- Madsen et al., 2015)	Not investigated/described*
latency	Increased M50 (MEG P1) latency (Oram Cardy et al., 2008)	Not investigated/described*
N1 amplitude	Decreased N1 amplitude (Brandwein et al., 2015; Bruneau et al., 1999; Gandal et al., 2010; Seri et al., 1999) *Normal N1 amplitude* (Ceponiene et al., 2003; Madsen et al., 2015)	Increased N1/M100 (MEG N1) amplitude (Castrén et al., 2003; Rojas et al., 2001; St Clair et al., 1987; Van der Molen et al., 2012a,b)
latency	Increased N1/M100 (MEG N1) latency (Gage et al., 2003; Gandal et al., 2010; Korpilahti et al., 2007; Roberts et al., 2010) *Normal N1 latency* (Bruneau et al., 1999; Ceponiene et al., 2003; Madsen et al., 2015)	Decreased M100 latency (MEG N1) (Rojas et al., 2001) *Normal N1 latency* (Van der Molen et al., 2012a,b)
P2 amplitude	Not investigated/described*	Increased P2 amplitude (Van der Molen et al., 2012b) *Normal P2 amplitude* (Van der Molen et al., 2012a)
latency	Not investigated/described*	*Normal P2 latency* (Van der Molen et al., 2012a,b)
N2 amplitude	Decreased N2 amplitude (Lepisto et al., 2005)	Increased N2b amplitude (Van der Molen et al., 2012a,b)
latency	*Normal N2 latency* (Lepisto et al., 2005)	Increased N2b latency (Van der Molen et al., 2012a,b)
P3a,b amplitude (pure tones)	Increased P3a amplitude (childhood- Ferri et al., 2003) Decreased P3a amplitude (young adult- Ferri et al., 2003) *Normal P3a amplitude* (Lepisto et al., 2005, 2006)	Decreased P3a,b amplitude (Van der Molen et al., 2012a,b)
amplitude (speech-like stimuli)	Decreased P3a amplitude (Ceponiene et al., 2003; Lepisto et al., 2005, 2006)	Not investigated/described*
P1 (P50) suppression	Decreased P1 suppression (Orekhova et al., 2008); (Madsen et al., 2015) *Normal P1 suppression* (Kemner et al., 2002; Madsen et al., 2015; Magnee et al., 2009)	Not investigated/described*
Startle reactivity, prepulse inhibition and startle habituation		
Acoustic startle response magnitude	Increased startle magnitude (Chamberlain et al., 2013; Dichter et al., 2010; Kohl et al., 2014; Takahashi et al., 2016; Wilbarger et al., 2009) *Normal startle magnitude* (Bernier et al., 2005; McAlonan et al., 2002; Salmond et al., 2003; Sterling et al., 2013; Yuhas et al., 2011)	*Normal startle magnitude* (Frankland et al., 2004)
latency	Increased startle latency (Ornitz et al., 1993; Takahashi et al., 2016; Yuhas et al., 2011) *Normal startle latency* (Bernier et al., 2005)	*Normal startle latency* (Yuhas et al., 2011)
PPI	Decreased PPI (adults (McAlonan et al., 2002; Perry et al., 2007)) Increased PPI (children (Madsen et al., 2014)) *Normal PPI (adults and children* (Kohl et al., 2014; Oranje et al., 2013b; Ornitz et al., 1993; Takahashi et al., 2016; Yuhas et al., 2011))	Decreased PPI (Frankland et al., 2004; Yuhas et al., 2011)
Habituation	Decreased habituation of ASR (Ornitz et al., 1993; Perry et al., 2007)	Not investigated/described*
Mismatch negativity		

Objective measure of auditory sensory processing	Autism Spectrum Disorder	Fragile X syndrome
Pure tone-frequency deviant	Decreased MMN (Abdeltawwab and Baz, 2015; Dunn et al., 2008) Increased MMN (Ferri et al., 2003) Normal MMN (Jansson-Verkasalo et al., 2003; Weismuller et al., 2015)	Decreased MMN (pure tone frequency deviant) (Van der Molen et al., 2012b)
Pure tone-duration deviant	Decreased MMN (Lepisto et al., 2005, 2006) *Normal MMN* (Weismuller et al., 2015)	Not investigated/described*
Speech-like stimuli-frequency deviant, word/vowel change	Decreased MMN (Kuhl et al., 2005; Kujala et al., 2010; Ludlow et al., 2014) Increased MMN (Korpilahti et al., 2007; Lepisto et al., 2005, 2006) *Normal MMN* (Ceponiene et al., 2003; Kasai et al., 2005; Oram Cardy et al., 2005; Weismuller et al., 2015)	Not investigated/described*
Speech-like stimuli-duration deviant	Decreased MMN (Lepisto et al., 2006) *Normal MMN* (Lepisto et al., 2005).	Not investigated/described*
MMN-all stimuli	Decreased MMN lateralization (Korpilahti et al., 2007; Kuhl et al., 2005; Weismuller et al., 2015) Abnormal MMN lateralization (Jansson-Verkasalo et al., 2003; Lepisto et al., 2006)	Not investigated/described*
Neural oscillations		
Baseline power of oscillations	Increased baseline delta (1–3 Hz), theta (4–8 Hz), beta (13–30 Hz) and gamma (30–80 Hz) power (Machado et al., 2013; Orekhova et al., 2007, 2008; van Diessen et al., 2014; Wang et al., 2013)	Increased baseline theta power (4–8 Hz) (Van der Molen and Van der Molen, 2013)
	Decreased baseline alpha (8–12 Hz) power (Machado et al., 2013; Orekhova et al., 2007, 2008; van Diessen et al., 2014; Wang et al., 2013)	Decreased baseline upper-alpha power (10–12 Hz) (Van der Molen and Van der Molen, 2013)
	Not investigated/described*	Increased resting theta functional connectivity (van der Molen et al., 2014)
	Not investigated/described*	Decreased resting upper alpha and beta functional connectivity (van der Molen et al., 2014)
Auditory-evoked power/synchrony of oscillations	Increased auditory-evoked gamma power (McFadden et al., 2012; Rojas et al., 2001, 2008) Decreased evoked synchrony across theta and gamma frequency bands (Jochaut et al., 2015)	Not investigated/described* Not investigated/described*

Table 2

Changes in sensory processing measures in rodent models that show analogies to the diagnostic symptoms of autism, including low social interactions, reduced vocalizations in social settings, and/or high levels of repetitive self-grooming. Findings in ASD and FXS are provided at the top of the table for comparison purposes.

	ERPs	MMN	Startle	PPI	Neural oscillations
Human disorders (refer to Table 1 for references)					
ASD	Decreased P1, N1, N2 and P3a amplitudes Increased N1 latency	Decreased (?)	Increased	?	Increased baseline theta and gamma Decreased baseline alpha power
FXS	Increased N1, P2 and N2b amplitudes	Decreased	=	Decreased	Increased baseline theta power Decreased baseline alpha power
ASD- and FXS-relevant mouse models					
Fmr1 KO	=Decreased habituation of N1 amplitude (Lovelace et al., 2016)	?	Decreased (Chen and Toth, 2001; Olmos-Serrano et al., 2011)	Increased (Chen and Toth, 2001; Frankland et al., 2004; Olmos-Serrano et al., 2011)	?
Prenatal VPA	Increased N1 latency (Gandal et al., 2010)	?	=(Schneider and Przewlocki, 2005; Schneider et al., 2006)	Decreased (Schneider and Przewlocki, 2005; Schneider et al., 2006)	?
MeCP2 T158A	Decreased N1 and P2 amplitudes Increased P1, N1 and P2 latencies (Goffin et al., 2011).	?	?	?	Increased baseline gamma power Decreased evoked theta, alpha and gamma power/ITC (Goffin et al., 2011)
MeCP2 +/−	Increased N1 amplitude Increased P2 latency (Liao et al., 2012)	?	Decreased (Chao et al., 2010; Samaco et al., 2008; Samaco et al., 2013)	Increased (Chao et al., 2010; Samaco et al., 2008; Samaco et al., 2013)	Increased evoked gamma power/ITC (Liao et al., 2012)
MeCP2 (interneuron KO)			Decreased (Chao et al., 2010)	Increased (Chao et al., 2010)	Decreased evoked theta, alpha and gamma power/ITC (Goffin et al., 2014)
C58/J	?	?	Decreased (Moy et al., 2014)	Increased (Moy et al., 2014)	?
Ephrin-A2/-A3 KO	?	?	Decreased (Wurzman et al., 2015)	Increased (Wurzman et al., 2015)	?
Gabrb3 +/−	?	?	Decreased (DeLorey et al., 2011)	Increased (DeLorey et al., 2011)	?
BK channel KO	?	?	Decreased (Typlt et al., 2013a)	Decreased (Typlt et al., 2013a)	?
P2 × 4 receptor KO	?	?	Decreased (Wyatt et al., 2013)	Decreased (Wyatt et al., 2013)	?
NL-3 mutant (R451C)	?	?	Decreased (Chadman et al., 2008)	=(Chadman et al., 2008)	?
NL-3 KO	?	?	=(Radyushkin et al., 2009)	=(Radyushkin et al., 2009)	?
BTBR T+ Itpr3 tf/J	?	?	=(Silverman et al., 2010)	=(Silverman et al., 2010)	?
16p11.2 +/−	? N/A	? N/A	=(Brunner et al., 2015) *mice deaf* (Portmann et al., 2014; Yang et al., 2015)	=(Brunner et al., 2015) *mice deaf* (Portmann et al., 2014; Yang et al., 2015)	? N/A

	ERPs	MMN	Startle	PPI	Neural oscillations
PDGFR-β KO	?	?	=(Nakamura et al., 2015; Nguyen et al., 2011)	Decreased (Nakamura et al., 2015; Nguyen et al., 2011)	Decreased gamma power and ITC (Nakamura et al., 2015; Nguyen et al., 2011)
Neurexin-1α KO	?	?	=(mouse) (Etherton et al., 2009) Increased (rat) (Esclassan et al., 2015)	Decreased (mouse) (Etherton et al., 2009) =(rat) (Esclassan et al., 2015)	?
PWS-IC(+/−)	?	?	Increased (Relkovic et al., 2010)	Decreased (Relkovic et al., 2010)	?
Th(tk-)/th (tk-)	?	?	Increased (Klejbor et al., 2009)	Decreased (Klejbor et al., 2009)	?
Npas4-KO	?	?	Increased (Coutellier et al., 2012)	Decreased (Coutellier et al., 2012)	?
Cntnap2 KO	?	?	=(Brunner et al., 2015)	Increased (Brunner et al., 2015)	?
Nrcam-KO	?	?	=(Moy et al., 2009)	Decreased (males) (Moy et al., 2009)	?
Shank3	?	?	=(Kouser et al., 2013)	=(Kouser et al., 2013)	?

KO – knockout, ITC – inter-trial coherence, N/A – not applicable.

Table 3

Changes in sensory processing measures in rodent models of disrupted excitatory/inhibitory balance that recapitulate ASD phenotypes. Findings in ASD and FXS are provided at the top of the table for comparison purposes.

	ERPs	MMN	Startle	PPI	Neural oscillations
Human disorders (refer to Table 1 for references)					
ASD	Decreased P1, N1, N2 and P3a amplitudes Increased N1 latency	Decreased (?)	Increased	?	Increased baseline theta and gamma Decreased baseline alpha power
FXS	Increased N1, P2 and N2b amplitudes	Decreased	=	Decreased	Increased baseline theta power Decreased baseline alpha power
ASD- and FXS-relevant mouse models					
GluN1$^{neo-/-}$	Increased N1 latency (Gandal et al., 2012a)	?	Increased (Duncan et al., 2004; Gandal et al., 2012a,b; Moy et al., 2014)	Decreased (Duncan et al., 2004; Gandal et al., 2012a,b; Moy et al., 2014)	Increased baseline theta and gamma Decreased evoked gamma power/ITC (Gandal et al., 2012b)
PV-selective GluN1 KO	Increased N1 latency (Billingslea et al., 2014; Saunders et al., 2013)	?	?	= (Carlén et al., 2012)	Increased baseline gamma (Billingslea et al., 2014; Carlén et al., 2012)
NMDAR blockade	Increased N1 latency (Saunders et al., 2012)	Decreased (Ehrlichman et al., 2008)	Increased (Bakshi and Geyer, 1998; Bast et al., 2000)	Decreased (Bakshi and Geyer, 1998; Bast et al., 2000)	Increased baseline gamma power Decreased evoked gamma power/ITC (Saunders et al., 2012)

KO – knockout, ITC – inter-trial coherence.