Article:
Dickinson, A., Jones, M. and Milne, E. (2016) Measuring neural excitation and inhibition in autism: different approaches, different findings and different interpretations. Brain Research. ISSN 0006-8993

https://doi.org/10.1016/j.brainres.2016.07.011

Measuring neural excitation and inhibition in autism: different approaches, different findings and different interpretations.

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Abstract

The balance of neural excitation and inhibition (E/I balance) is often hypothesised to be altered in autism spectrum disorder (ASD). One widely held view is that excitation levels are elevated relative to inhibition in ASD. Understanding whether, and how, E/I balance may be altered in ASD is important given the recent interest in trialling pharmacological interventions for ASD which target inhibitory neurotransmitter function. Here we provide a critical review of evidence for E/I balance in ASD. We conclude that data from a number of domains provides support for alteration in excitation and inhibitory neurotransmission in ASD, but when considered collectively, the available literature provide little evidence to support claims for either a net increase in excitation or a net increase in inhibition. Strengths and limitations of available techniques are considered, and directions for future research discussed.

1. Introduction

Autism spectrum disorder (ASD) is diagnosed based on the presence of impairments in social interaction and communication, accompanied by restricted and repetitive behaviours (American Psychiatric Association, 2013). ASD has been reported to affect around 1 in 68 children (Christensen et al., 2016), yet the precise etiology of the condition is unknown. One hypothesis regarding the pathophysiology of ASD centres on alteration in the balance of neural excitation and inhibition (E/I balance), which is mediated by the effective magnitude and timing of excitatory and inhibitory synaptic inputs to a cortical neuron or network. Due to the widespread consequences that altered E/I balance has for brain function and behaviour (Haider, Häusser, & Carandini, 2013), E/I imbalance has been suggested as a possible explanation for the behavioural, cognitive and perceptual differences observed in those with ASD. While most accounts suggest that excitation may be increased relative to inhibition in ASD (Coghlan et al., 2012; Hussman, 2001; Markram, Rinaldi, & Markram, 2007; Rubenstein & Merzenich, 2003), others suggest that inhibition may be increased in ASD relative to excitation (Bertone, Mottron, Jelenic, & Faubert, 2005; Gustafsson, 1997a). When evaluating the diverse results of studies which assess E/I balance in ASD, one thing which should be considered is the possibility that an imbalance (or the direction of such imbalance) may not manifest in a ubiquitous way across the condition. ASD is highly heterogeneous, and likely emerges as the consequence of diverse neurobiological sequelae, as is suggested by the many different genetic abnormalities associated with ASD (Miles, 2011). It is therefore possible that sub-groups of individuals with ASD have specific differences in E/I balance that are not universal, and may contribute to the heterogeneity of the condition.

The suggestion that E/I balance is altered in ASD, and in particular the hypothesis that excitation is increased relative to inhibition in ASD, is largely based on the observation that seizure disorders such as epilepsy frequently co-occur with ASD (Rubenstein & Merzenich, 2003). Estimates of the prevalence rates of epilepsy in ASD range from 5-46% (Bryson, Clark, & Smith, 1988; Hughes & Melyn, 2005) and converge at around 30% (Canitano, 2007). Subclinical epileptiform activity in the electroencephalography (EEG) is also present in a high proportion of children with ASD (Chez et al., 2006; Hughes and Melyn,

2005; McVicar et al., 2005; Rossi et al., 1995) with one study suggesting that up to 85% of children display such activity (Yasuhara, 2010). However, epilepsy does not arise simply due to an increase in neuronal excitation or decrease in inhibition (Engel, 1996) and seizures occur as a result of complicated neuronal interactions that can differ both within and between patients. In addition, not all individuals with ASD have co-occurring seizures, and not all individuals with epilepsy have ASD. This suggests that there may be different neural pathways to the symptoms of ASD, and that the neural changes associated with epilepsy do not necessarily lead to ASD. It also highlights the importance of obtaining data that directly measures E/I balance in ASD.

Over the last decade, myriad research papers from a range of disciplines have attempted to test the hypothesis that E/I balance is altered in ASD. Examples include: studies that measure gamma-Aminobutyric acid (GABA) and glutamate (the main inhibitory and excitatory neurotransmitters) receptors in post-mortem brain tissue (e.g. Fatemi, Reutiman, et al.,2009); studies that use Magnetic Resonance Spectroscopy (MRS) to measure GABA and glutamate levels in vivo (e.g. Rojas et al., 2014), and studies that measure aspects of perception from which alterations in E/I balance are inferred (Dickinson et al. 2016, Robertson et al. 2016). A number of excellent methodologically-specific review articles evaluating some of this work have been published recently. For example Rojas et al. (2015) reviewed MRS studies that measure glutamate and GABA levels in ASD, and Pizzarelli and Cherubini (2011) reviewed cellular abnormalities that implicate E/I imbalance in animal models of ASD (see also Coghlan et al., 2012). Here we take a broader approach, and rather than focusing on data arising from a specific technique or field, we review data arising from the range of methodologies that have been used to investigate, or infer, E/I balance in ASD.

2. Empirical Evidence for E/I imbalance in ASD

We start the review with a description of neuro-architectural differences associated with E/I imbalance in ASD, including cellular abnormalities measured from post-mortem brain tissue and mini-columnar structure. We then consider studies that measure excitatory and inhibitory neurotransmitters, from both blood plasma and brain, before describing how differences in gamma-band activity recorded by magnetoencephalography

(MEG) or EEG, and atypical perceptual function, have been considered to infer E/I imbalance in ASD. An emerging theme from this review is that measuring E/I balance in humans is not straightforward. Many of the claims made regarding altered E/I balance in ASD rely on assumptions, such as assumptions about how alteration of one feature, such as cortical neurotransmitter levels or synaptic protein levels may affect net E/I balance, or assumptions about the extent to which a certain perceptual task reflects E/I balance. Nevertheless, the collective findings from this body of work certainly imply that E/I balance may be disrupted in ASD, although we would argue that the strength of available evidence is not sufficient to accurately describe the direction of such an imbalance (i.e. whether excitation is increased or reduced relative to inhibition).

2.1 Cellular Abnormalities

Arguably, the most compelling evidence for altered E/I balance in ASD comes from studies that have identified abnormalities in anatomical features that are associated with controlling neural excitation and inhibition in ASD. Although many cellular abnormalities have been reported in ASD, this discussion will only highlight examples of the cellular abnormalities found in ASD that are considered to implicate E/I balance (for a more thorough review and diagram of E/I balance at a cellular level, see Coghlan et al., 2012). See table 1 for a summary of the studies described in this section.

Neural transmission relies on a complex system of neurotransmitter generation, release, reception and re-uptake. In ASD, abnormalities have been found in many of the components of this system. For example Fatemi, Reutiman et al. (2009) found reductions in $GABA_A$ receptor density in parietal, cerebellar and superior frontal regions in ASD (see also Blatt et al., 2001; Fatemi, Folsom et al., 2009; Fatemi et al., 2014, Oblak et al., 2011, 2010, 2009), and AMPA-type glutamate receptor density was found to be reduced in the cerebellum of individuals with ASD (Purcell, Jeon, Zimmerman, Blue, & Pevsner, 2001). There is also evidence that the synthesis of GABA and glutamate is altered in ASD. Glutamic acid decarboxylase (GAD) is an enzyme responsible for catalysing the decarboxylation of glutamic acid to form GABA and exists in two isoforms: 65 and 67 (GAD65; GAD67). Post mortem studies have revealed that both GAD65 and GAD 67 are decreased in the cerebellum and parietal cortex of individuals with ASD (Fatemi et al., 2002; Yip,

Soghomonian, & Blatt, 2007). In addition, Shimmura et al. (2013) found that enzymes associated with the glutamate-glutamine cycle are decreased in post mortem brain tissue of individuals with ASD, thus also suggesting a dysfunction in excitatory neurotransmission in ASD.

These studies provide strong evidence for the position that E/I balance is likely to be altered in ASD, however, it is hard to predict how a disruption in either receptor density and / or enzyme levels would affect overall E/I balance in ASD. For instance, low levels of GABA receptor expression may be compensated for by higher levels of GABA being released from presynaptic terminals (Dhossche et al., 2002; Fatemi, Reutiman et al., 2009). Therefore, while this research strongly implicates alteration in mechanisms underpinning E/I balance in ASD, it does not speak clearly to the direction of such an imbalance. Numerous animal models that mimic some aspects of the behavioural symptoms of ASD also display alterations in E/I balance, with altered GABAergic and glutamatergric transmission observed in several studies (for a review see Pizarelli & Cherubini, 2011). However, whilst Markram et al. (2008) find defective inhibitory transmission in one mouse model of ASD, other models reveal increased inhibitory transmission, or decreased glutamatergic transmission (Blundell et al., 2010; Tabuchi et al., 2007), demonstrating that even animal models display variable and conflicting results regarding E/I balance in ASD.

Table 1. Post-mortem studies of cellular abnormalities in ASD.

Study (Year)	**Participants** Group: N (mean age in years)	**Measure**	**Finding**	**Interpretation regarding E/I balance in ASD.**
Blatt et al. (2001)	ASD: 4 (20) NT: 3 (19.7)	$GABA_A$ receptor density in hippocampus.	Decreased $GABA_A$ receptor density in ASD.	Decreased inhibition.
Fatemi et al. (2002)	ASD: 5 (25.2) NT: 8 (23.5)	Levels of GAD65 & GAD67 measured in cerebellum.	Decreased GAD65 and GAD 67 levels in ASD.	Decreased inhibition.
Fatemi et al. (2002)	ASD: 5 (21.6) NT: 4 (21.6)	Levels of GAD65 & GAD67 measured in parietal cortex.	Decreased GAD65 and GAD 67 levels in ASD.	Decreased inhibition.
Fatemi et al. (2014)	ASD: 7 (24.1) NT: 6 (23.7)	Protein expression of $GABA_A$ receptor subunits in parietal cortex.	No group differences.	No difference.
Fatemi et al. (2014)	ASD: 7 (24.9) NT: 1 (26.6)	Protein expression of $GABA_A$ receptor subunits in the cerebellum.	No group differences.	No difference.
Fatemi et al. (2014)	ASD: 6 (23) NT: 3 (26)	Protein expression of GABA receptor subunits in frontal cortex.	Reduced protein expression for several $GABA_A$ receptor subunits.	Decreased inhibition.
Fatemi, Folsom et al. (2009)	ASD: 6 (24) NT: 10 (24)	$GABA_B$ receptor density in cerebellum.	Decreased $GABA_B$ receptor density in ASD.	Decreased inhibition.
Fatemi,	ASD: 8 (23.5)	$GABA_B$	Decreased $GABA_B$ receptor	Decreased

Folsom et al. (2009)	NT:6 (23.7)	receptor density in parietal cortex.	density in ASD.	inhibition.
Fatemi, Folsom et al. (2009)	ASD: 6 (23) NT: 3 (26)	$GABA_B$ receptor density in frontal cortex.	Decreased $GABA_B$ receptor density in ASD.	Decreased inhibition.
Fatemi, Reutiman et al. (2009)	ASD: 6 (24) NT: 11 (26.9)	$GABA_A$ receptor density in cerebellum.	Decreased $GABA_A$ receptor density in ASD.	Decreased inhibition.
Fatemi, Reutiman et al. (2009)	ASD: 8 (23.5) NT: 6 (23.7)	$GABA_A$ receptor density in parietal cortex.	Decreased $GABA_A$ receptor density in ASD.	Decreased inhibition.
Fatemi, Reutiman et al. (2009)	ASD: 6 (23) NT: 3 (26)	$GABA_A$ receptor density in frontal cortex.	Decreased $GABA_A$ receptor density in ASD.	Decreased inhibition.
Oblak et al. (2009)	ASD: 7 (21.4) NT: 9 (25.9)	$GABA_A$ receptor density measurement in anterior cingulate cortex.	Decreased $GABA_A$ receptor density in anterior cingulate cortex and fusiform gyrus in ASD.	Decreased inhibition.
Oblak et al. (2010)	ASD: 7 (21.4) NT: 9 (25.8)	$GABA_B$ receptor density in anterior cingulate cortex.	Decreased $GABA_B$ receptor density in ASD.	Decreased inhibition.
Oblak et al. (2010)	ASD: 6 (21.3) NT: 7 (27.1)	$GABA_B$ receptor density in posterior cingulate cortex.	Decreased $GABA_B$ receptor density in ASD.	Decreased inhibition.
Oblak et al. (2010)	ASD: 8 (25) NT: 10 (26.1)	$GABA_B$ receptor density in fusiform gyrus.	Decreased $GABA_B$ receptor density in ASD.	Decreased inhibition.
Oblak et al. (2011)	ASD: 7 (21.4) NT: 7 (25.9)	$GABA_A$ receptor density in	Decreased $GABA_A$ receptor density in ASD.	Decreased inhibition.

		posterior cingulate cortex.		
Oblak et al. (2011)	ASD: 9 (24) NT: 10 (26.1)	$GABA_A$ receptor density in fusiform gyrus.	Decreased $GABA_A$ receptor density in ASD.	Decreased inhibition.
Purcell et al. (2001)	ASD: 10 (19) NT: 16 (23.3)	AMPA-type glutamate receptor density in cerebellum.	AMPA-type glutamate receptor density was decreased in ASD.	Decreased excitation.
Purcell et al. (2001)	ASD: 4 (21.3) NT: 7 (20.8)	AMPA-type glutamate receptor density in frontal cortex.	No group difference.	No difference.
Purcell et al. (2001)	ASD: 3 (22) NT: 6 (23.5)	AMPA-type glutamate receptor density in caudate-putamen.	No group difference.	No difference.
Shimmura et al. (2013)	ASD: 7 (15.9) NT: 13 (15.8)	Levels of glutaminase measured in anterior cingulate cortex.	Decreased glutaminase levels in ASD.	Decreased excitation.
Yip et al. (2007)	ASD: 8 (21.5) NT: 8 (23.4).	Levels of GAD67 measured in cerebellum.	Decreased GAD67 levels in ASD.	Decreased inhibition.

NT neurotypical.

2.2 Cortical Minicolumns

Cortical minicolumns are vertical columns of pyramidal cells which ascend radially through layers VI and II of cortex. They are found in all regions of cortex and constitute the smallest neocortical module capable of processing information (Mountcastle, 1997). Changes in cortical minicolumns reported in ASD have been linked to E/I balance via the assumption that the precise organisation of the connectivity of the cortex could influence the effective balance of excitation and inhibition. However, while post mortem analysis has revealed that individuals with ASD show minicolumnar abnormalities across widespread regions of the cortex, the precise nature of such abnormality is not consistent across all studies. See table 2 for a summary of these data. For example, some studies have found reduced neuropil space and narrower minicolumn width in frontal and temporal brain regions in ASD (Buxhoeveden et al., 2007; Casanova, Buxhoeveden, Switala, & Roy, 2002a; Casanova, Buxhoeveden, Switala, & Roy, 2002b; Casanova et al., 2006), whereas a recent study has reported wider minicolumns in sensory, frontal and parietal cortical areas in ASD (McKavanagh, Buckley, & Chance, 2015).

Neuropil space surrounds the minicolumn core and contains GABAergic inhibitory interneurons (Favorov & Kelly, 1994) which insulate the excitatory flow in the core from the activity of surrounding minicolumns (de Felipe, 1999). It has therefore been postulated that reduced neuropil space would limit the effectiveness of this inhibitory ‘sheath’, and lead to reduced neural inhibition in ASD (Casanova, Buxhoeveden, & Gomez, 2003). However, in contrast to the suggestion that narrower minicolumns in ASD are associated with reduced inhibition, computational modelling work (Gustafsson, 1997b) and experimental studies in cats (Hensch, 2007), have shown that in fact narrower minicolumns could be associated with increased inhibition.

Minicolumns are a major aspect of neural architecture, and it is likely that differences in their structure would have widespread consequences for E/I balance. Therefore, the finding of altered minicolumns in ASD is important. However, despite a tendency in the literature for researchers to cite minicolumn abnormalities

as evidence for E/I imbalance, and typically increased excitation relative to inhibition, in ASD, it is clear that there is no consensus in the literature regarding how minicolumns are altered in ASD, nor how altered minicolumnar structure may relate to E/I balance.

Table 2. Studies of cortical minicolumns in ASD.

Study (Year)	**Participants** Group: N (mean age in years)	**Measure**	**Finding**	**Interpretation regarding E/I balance in ASD[a].**
Buxhoeveden et al. (2007)	ASD: 2 (22) NT: 5 (35.2)	Minicolumn width in frontal cortex.	Decreased minicolumn width in ASD.	Increased inhibition.
Buxhoeveden et al. (2007)	ASD: 2 (22) NT: 5 (35.2)	Minicolumn width in primary visual cortex.	No group difference.	No difference.
Casanova et al. (2002a)	ASD: 9 (12) NT: 4 (not reported)	Minicolumn width in temporal lobe.	Decreased minicolumn width in ASD.	Increased inhibition.
Casanova et al. (2002a)	ASD: 9 (12) NT: 4 (not reported)	Minicolumn width in prefrontal cortex.	Decreased minicolumn width in ASD.	Increased inhibition.
Casanova et al. (2002b)	ASD: 1(79) NT: 11 (72.09)	Minicolumn width in superior-temporal cortex.	Decreased minicolumn width in ASD.	Increased inhibition.
Casanova et al. (2002b)	ASD 1: (22) NT: 7 (21.14)	Minicolumn width in middle-temporal cortex.	No group difference.	No difference.
Casanova et al. (2002b)	ASD 1: (22) NT: 7 (21.14)	Minicolumn width in frontal cortex.	No group difference.	No difference.
Casanova et al. (2002b)	ASD 1: (22) NT: 7 (21.14)	Minicolumn width in superior-temporal cortex.	No group difference.	No difference.
Casanova et al. (2006)	ASD: 6 (12.3) NT: 6 (12.8)	Minicolumn width in somatosensory cortex.	Decreased minicolumn width in ASD.	Increased inhibition.

Casanova et al. (2006)	ASD: 6 (12.3) NT: 6 (12.8)	Minicolumn width in motor cortex.	Decreased minicolumn width in ASD.	Increased inhibition.
Casanova et al. (2006)	ASD: 6 (12.3) NT: 6 (12.8)	Minicolumn width in visual cortex.	Decreased minicolumn width in ASD.	Increased inhibition.
Casanova et al. (2006)	ASD: 6 (12.3) NT: 6 (12.8)	Minicolumn width in frontal association cortex.	Decreased minicolumn width in ASD.	Increased inhibition.
McKavanagh et al. (2015)	ASD: 28 (16.1) NT: 25 (34)	Minicolumn width in auditory cortex.	Increased minicolumn width in ASD.	Decreased inhibition.
McKavanagh et al. (2015)	ASD: 28 (16.1) NT: 25 (34)	Minicolumn width in auditory association cortex.	Increased minicolumn width in ASD.	Decreased inhibition.
McKavanagh et al. (2015)	ASD: 28 (16.1) NT: 25 (34)	Minicolumn width in orbital frontal cortex.	Increased minicolumn width in ASD.	Decreased inhibition.
McKavanagh et al. (2015)	ASD: 28 (16.1) NT: 25 (34)	Minicolumn width in inferior parietal lobe.	Increased minicolumn width in ASD.	Decreased inhibition.

NT neurotypical.

[a] Results are interpreted in line with evidence that wider minicolumns reflect decreased inhibition (Gustafsson, 1997b, Hensch, 2007). However, see the text for a full discussion of the interpretation of these findings.

2.3 Blood Measurement

Several ASD studies have attempted to quantify glutamate and GABA levels via blood measurements, although results are inconsistent (see table 3 for a summary of these studies). Blood plasma glutamate levels have been found to be increased (Hassan et al., 2013) and platelet levels of its precursor glutamine, decreased (Rolf, Haarmann, Grotemeyer, & Kehrer, 1993) in participants with ASD compared to neurotypical controls. Similarly, whilst Dhossche et al (2002) reported higher blood plasma GABA levels in children with ASD, decreased platelet levels of GABA have also been reported (Rolf et al., 1993). Further difficulty in interpretation of such studies arises from the fact that amino acid neurotransmitters do not easily cross the blood-brain barrier, and as such it is difficult to interpret the results of studies which measure glutamate and GABA levels in this way in terms of neural E/I balance within the brain (see also Rojas, Becker & Wilson, 2015).

Table 3. Blood measurement studies of E/I balance in ASD.

Study (Year)	**Participants** Group: N (mean age in years)	**Measure**	**Finding**	**Interpretation regarding E/I balance in ASD.**
Dhossche et al. (2002)	ASD: 9 (7.8) ADHD: 9 (10.5)	Blood plasma levels of GABA.	Increased GABA levels in ASD.	Increased inhibition.
Hassan et al. (2013)	ASD: 10 (11.4) NT: 10 (11.3).	Blood plasma levels of glutamate.	Increased glutamate levels in ASD.	Increased excitation.
Rolf et al. (1993)	ASD: 18 ASD (9.9) NT: 14 (11.5)	Platelet levels of glutamine (glutamate precursor).	Decreased glutamine levels in ASD.	Decreased excitation.
Rolf et al. (1993)	ASD: 18 ASD (9.9) NT: 14 (11.5)	Platelet levels of GABA.	Decreased GABA levels in ASD.	Decreased inhibition.

NT neurotypical; ADHD attention deficit hyperactivity disorder

2.4 Magnetic Resonance Spectroscopy (MRS) Studies

By contrast, MRS allows the quantification of different neurochemicals including excitatory and inhibitory neurotransmitters within brain tissue and has therefore been used to measure cortical levels of both glutamate and GABA in individuals with ASD. When measuring glutamate, many MRS studies combine the resonances of glutamate and its precursor, glutamine into one single measure: Glx. A comprehensive review of this work has been published recently (Rojas, Becker & Wilson, 2015) therefore here we provide a brief overview of the results of studies which have measured either GABA, glutamate or Glx in ASD, and consider what can be learnt about E/I balance in ASD from this work. These studies are summarized in table 4.

2.4.1 Glutamate / Glx

Several studies have measured resting levels of glutamate and/or Glx levels in ASD, however, results vary with respect to whether glutamate / Glx is increased or decreased in ASD compared to neurotypical controls. For example, glutamate/Glx levels have been found to be increased in several regions in individuals with ASD compared to controls, including the ACC (Bejjani et al., 2012; Hassan et al., 2013); hippocampus (Page et al., 2006); putamen (Doyle-Thomas et al., 2014); Heschl's gyrus (Brown, Singer, Hepburn & Rojas, 2013); and the cerebellum; striatum and frontal lobe (Hassan et al., 2013). However, other studies have found decreased glutamate/Glx in ASD in regions including the ACC (Bernardi et al., 2011; van Elst, Maier, Fangmeier, & Endres, 2014) the basal ganglia (Horder et al., 2013); frontal and occipital cortex, the cerebellum (Devito et al., 2007) and white matter (Corrigan et al., 2013). Yet other studies have found no significant differences in glutamate / Glx levels between individuals with and without ASD in several different brain regions including parietal lobes (Horder et al., 2013; Page et al., 2006), frontal lobes (Horder et al., 2013) temporal lobes (Devito et al., 2007), and occipital lobes (Robertson, Ratai, & Kanwisher, 2015); the thalamus (Bernardi et al., 2011; Doyle-Thomas et al., 2014; Hardan et al., 2008); hippocampus (Joshi et al., 2012); and cerebellum (van Elst et al., 2014). Therefore, the literature regarding glutamate/Glx levels in ASD is mixed. Even measuring glutamate/Glx levels from the same structure has yielded inconsistent results (c.f. DeVito et al., 2007; Hassan et al., 2013).

2.4.2 GABA

Fewer studies have attempted to measure cortical GABA levels in ASD. Although results appear to be more consistent than when measuring glutamate/Glx. For example, decreased GABA levels in individuals with ASD compared to controls have been reported in motor (Gaetz et al., 2014) and auditory cortex (Gaetz et al., 2014; Rojas, Singel, Steinmetz, Hepburn, & Brown, 2014), and in the ACC (Cochran et al., 2015), although Brix et al. (2015) found no differences in GABA levels in the ACC. Other regions, such as the occipital cortex show no differences in GABA levels between participants with and without ASD (Gaetz et al., 2014; Robertson et al., 2015).

2.4.3 Implications for E/I balance

There is no clear picture regarding how glutamate / Glx levels may be altered in ASD. There is more support for reduced cortical GABA levels in ASD, although this does not appear to be consistent across the cortex. Nevertheless, it is difficult to predict the resultant effect of any alteration in neurotransmitter levels on the net balance of E/I due to the complex interactions between the level of a single inhibitory neurotransmitter and compensatory excitatory mechanisms (Levin & Nelson, 2015). Even within an individual, neurotransmitter levels vary between different cortical areas (Gao et al., 2013), and over time (e.g. with the menstrual cycle, Epperson et al., 2002) adding further complexity to the task of investigating E/I balance by studying neurotransmitter levels alone. There are also limitations to the MRS technique. For instance, GABA measurement in particular is difficult due to overlap between its resonance spectra and those of creatine and other macromolecules (Puts & Edden, 2012), and it can be difficult to localise the relatively large area of brain (typically $3cm^3$) measured using MRS to a particular brain structure, which may lead to differences between studies. Therefore, while the available evidence provides some evidence that excitatory and inhibitory neurotransmitter levels may be altered in ASD relative to neurotypical controls, the precise nature of any such alteration, and the direct consequence of this for E/I imbalance remain unclear.

Table 4. MRS studies of E/I balance in ASD.

Study (Year)	Participants Group: N (mean age in years)	Measure	Finding	Interpretation regarding E/I balance in ASD.
Bejjani et al. (2012)	ASD: 8 (11.2) NT: 10 (13.2)	Glx levels measured in anterior cingulate cortex.	Increased Glx in ASD.	Increased excitation.
Bejjani et al. (2012)	ASD: 26 (10.2) NT: 16 (11.8)	Glx levels measured in left and right anterior cingulate cortex.	Increased Glx in ASD.	Increased excitation.
Bernardi et al. (2011)	ASD: 14 (29.2) NT: 14 (29.7)	Glutamate levels in temporoparietal junction.	No group differences.	No difference.
Bernardi et al. (2011)	ASD: 14 (29.2) NT: 14 (29.7)	Glutamate levels in anterior cingulate cortex.	Glutamate levels decreased in ASD.	Decreased excitation.
Bernardi et al. (2011)	ASD: 14 (29.2) NT: 14 (29.7)	Glutamate levels in thalamus.	No group differences.	No difference.
Bernardi et al. (2011)	ASD: 14 (29.2) NT: 14 (29.7)	Glutamate levels in intra parietal cortex.	No group differences.	No difference.
Brix et al. (2015)	ASD: 14 (10.2) NT: 24 (10.2)	GABA levels in anterior cingulate cortex.	No group differences.	No difference.
Brown et al. (2013)	ASD: 13 (36.89) NT: 15 (41.08)	Glx and glutamate levels measured in Heschl's gyrus.	Glx and glutamate levels increased in ASD.	Increased excitation.
Cochran et al. (2015)	ASD: 13 (14.9) NT: 14 (14.7)	GABA, glutamate and glutamine levels in anterior cingulate cortex.	Increased glutamine and decreased GABA levels in ASD.	Increased excitation.
Corrigan et al. (2013)	ASD: 45 (4) NT: 10 (3.8) Developmental Delay: 13 (3.9)	Glx levels in grey and white matter.	Decreased Glx levels in white matter in ASD.	Decreased excitation.
Corrigan et al. (2013)	ASD: 31 (6.6) NT: 18 (6.6) Developmental Delay: 14 (6.4)	Glx levels in grey and white matter.	No group difference.	No difference.
Corrigan et al. (2013)	ASD: 29 (9.6) NT: 29 (9.6)	Glx levels in grey and white matter.	No group difference.	No difference.

	Developmental Delay: 12 (9.5)			
De Vito et al. (2007)	ASD: 26 (9.8) NT: 29 (11.1)	Glx levels in frontal lobe.	Decreased Glx levels in ASD.	Decreased excitation.
De Vito et al. (2007)	ASD: 26 (9.8) NT: 29 (11.1)	Glx levels in temporal lobe.	No group difference.	No difference
De Vito et al. (2007)	ASD: 26 (9.8) NT: 29 (11.1)	Glx levels in occipital lobe.	Decreased Glx levels in ASD.	Decreased excitation.
De Vito et al. (2007)	ASD: 26 (9.8) NT: 29 (11.1)	Glx levels in the cerebellum.	Decreased Glx levels in ASD.	Decreased excitation.
Doyle-Thomas et al. (2014)	ASD: 20 (11.5) NT: 16 (12.9)	Glx levels measured in caudate.	No group differences.	No difference.
Doyle-Thomas et al. (2014)	ASD: 20 (11.5) NT: 16 (12.9)	Glx levels measured in thalamus.	No group differences.	No difference.
Doyle-Thomas et al. (2014)	ASD: 20 (11.5) NT: 16 (12.9)	Glx levels measured in putamen.	Increased Glx in ASD.	Increased excitation.
Gaetz et al. (2014)	ASD: 17 (11.5) NT: 15 (12.7)	GABA levels in left auditory cortex.	Decreased GABA levels in ASD.	Decreased inhibition.
Gaetz et al. (2014)	ASD:13 (12.2) NT: 11 (11.1)	GABA levels in left motor cortex.	Decreased GABA levels in ASD.	Decreased inhibition.
Gaetz et al. (2014)	ASD: 8 (13) NT:10 (13.3)	GABA levels left and right visual cortex.	No group differences.	No difference. .
Hardan et al. (2008)	ASD: 18 (11.6) NT: 16 (11.9)	Glutamate levels in the thalamus.	No group differences.	No difference.
Hassan et al. (2013)	ASD: 10 (11.4) NT: 10 (11.3)	Glutamate levels measured in bilateral anterior cingulate.	Increased glutamate in ASD.	Increased excitation.
Hassan et al. (2013)	ASD: 10 (11.4) NT: 10 (11.3)	Glutamate levels measured in left striatum.	Increased glutamate in ASD.	Increased excitation.
Hassan et al. (2013)	ASD: 10 (11.4) NT: 10 (11.3)	Glutamate levels measured in left cerebellar hemisphere.	Increased glutamate in ASD.	Increased excitation.

Hassan et al. (2013)	ASD: 10 (11.4) NT: 10 (11.3)	Glutamate levels measured in left frontal lobe.	Increased glutamate in ASD.	Increased excitation.
Horder et al. (2013)	ASD (ND): 15 (29) ASD (BP): 13 (27) NT: 14 (34)	Glx levels measured in basal ganglia.	Decreased Glx levels in ASD.	Decreased excitation.
Horder et al. (2013)	ASD (ND): 15 (29) ASD (BP): 13 (27) NT: 14 (34)	Glx levels measured in frontal cortex.	No group difference.	No difference.
Horder et al. (2013)	ASD (ND): 15 (29) ASD (BP): 13 (27) NT: 14 (34)	Glx levels measured in parietal cortex.	No group difference.	No difference.
Joshi et al. (2012)	ASD: 7 (14) ASD: 7 (NR)	Glutamate levels in anterior cingulate cortex.	Increased glutamate levels in ASD.	Increased excitation.
Joshi et al. (2012)	ASD: 7 (14) ASD: 7 (NR)	Glutamate levels in the hippocampus.	No group differences.	No difference.
Page et al. (2006)	ASD: 20 (35.6) NT: 13 (34.3)	Glx levels measured in right hippocampus.	Increased Glx in ASD.	Increased excitation.
Page et al. (2006)	ASD: 17 (35.6) NT: 19 (34.3)	Glx levels measured in right parietal cortex.	No group differences.	No difference.
Robertson et al. (2015)	ASD: 20 (29.61) NT: 21 (29.1)	GABA and Glx levels in occipital cortex.	No group differences.	No difference.
Rojas et al. (2014)	ASD: 17 (14.01) NT: 17 (12.44)	GABA levels in left auditory cortex.	Decreased GABA levels in ASD.	Decreased inhibition.
van Elst et al. (2014)	ASD: 29 (35.31) NT: 29 (35.79)	Glutamate and Glx levels measured in anterior cingulate cortex.	Glutamate and Glx levels decreased in ASD.	Decreased excitation.
van Elst et al. (2014)	ASD: 29 (35.31) NT: 29 (35.79)	Glutamate and Glx levels measured in left cerebellum.	No group difference.	No difference.

NT neurotypical; ND narrowly defined phenotype; BP broader phenotype.

2.5 High frequency neural oscillations (gamma-band activity)

Gamma-band activity (30+Hz) is thought to be generated by the activity of inhibitory GABA-ergic interneurons in neuronal networks involving excitatory pyramidal cells and inhibitory interneurons (Bartos, Vida, & Jonas, 2007; Cardin et al., 2009; Traub et al., 1998; Whittington, Traub, Kopell, Ermentrout, & Buhl, 2000; Whittington & Traub, 2003). A number of authors have therefore suggested that gamma activity recorded through either EEG or MEG provides insight into the dynamics of E/I balance at a network level (e.g. Snijders et al., 2013). The vast majority of studies investigating gamma activity in ASD have measured gamma power, i.e. changes in the magnitude of gamma amplitude associated with the presentation of a stimulus (e.g. evoked or induced gamma power), or spontaneous gamma power recorded while participants are awake but at-rest. All of the studies described in this section are summarized in table 5.

This work has shown that spontaneous gamma power is increased in ASD (Cornew et al., 2012; Edgar et al., 2015; Machado et al., 2013; Orekhova et al., 2008, 2007; van Diessen et al., 2015, although see Maxwell et al., 2013). However, what this suggests about E/I balance in less clear. Cardin et al. (2009) optogenetically activated fast spiking inhibitory interneurons and found that this selectively increased the power of spontaneous gamma band oscillations in rodent whisker barrel somatosensory cortex. Similarly, pharmaceutical manipulation to enhance GABA transmission in human participants with schizophrenia has been shown to lead to increased gamma band power (Lewis et al., 2008). Therefore spontaneous gamma power in ASD may reflect increased GABA levels. However, other evidence suggests that this may not be the case, as Yizhar and colleagues showed that optogenetically increasing excitation in the prefrontal cortex of mice resulted also in an increase in the spontaneous gamma power of the local field potential (Yizhar et al., 2011). Thus the relationship between E/I balance and spontaneous gamma power does not appear to be straightforward..

When considering papers that report task- or stimulus-related changes to gamma power in ASD, results are much less consistent. Changes in M/EEG spectral power elicited by stimuli can be divided into two main categories: evoked and induced (Galambos, Basar, & Bullock, 1992). Evoked activity is both phase-locked and time-locked to the onset of a stimulus; induced activity often occurs later than evoked activity, and

whilst it is time-locked it is not phase-locked to the stimulus. While several studies have found evoked gamma band power to be reduced in ASD (Edgar et al., 2015; Baruth et al., 2010; Rojas, Maharajh, Teale, & Rogers, 2008; Snijders et al., 2013; Stroganova et al., 2012; Sun et al., 2012; Wilson, Rojas, Reite, & Teale, 2007), other studies have found no group differences in evoked gamma power between individuals with and without ASD (Gandal et al., 2010; Milne, Scope, Pascalis, Buckley, & Makeig, 2009; Wright et al., 2012). Broadly speaking, when measured over the appropriate sensory cortices following the presentation of a visual or auditory stimulus, evoked gamma power tends to be reduced in participants with ASD compared to controls, although not all studies concur with this description (see David et al. (in press) for a review). With regard to induced gamma band power, both increases (Brown et al., 2005; Sokhadze study et al., 2009; Rojas et al., 2008), and decreases (Gross et al., 2012; Sun et al., 2012; Wright et al., 2012) have been found in individuals with ASD.

What do changes in evoked and / or induced gamma band power suggest about E/I balance in ASD? There is little existing data that allows us to confidently link evoked gamma power to E/I balance, although one study suggests that evoked gamma power may be associated with glutamate levels, as Lally et al. (2014) have reported a positive correlation between dynamic glutamate levels (measured using MRS) and evoked gamma band power (measured using EEG recorded from parietal and occipital electrodes; Lally et al., 2014). Therefore, evidence for reduced evoked gamma power may tentatively suggest decreased glutamate levels in ASD.

There are more studies that have investigated associations between E/I balance and induced gamma power, but findings are inconsistent. In line with the role of inhibitory interneurons in generating gamma band activity, a positive correlation between GABA levels in superior temporal sulcus (measured using MRS) and the power of induced gamma band oscillations has been reported (Balz et al., 2016), suggesting that increased induced gamma band power is associated with higher GABA levels. This position is also supported by pharmalogical manipulations of GABA, as administration of propofol (a GABA agonist) leads to an increase in induced gamma band power (Saxena, Muthukumaraswamy, & Diukova, 2013). However, other studies have not found any association between GABA levels (in occipital cortex) and induced gamma band power (Cousijn et al., 2014; Edden, Muthukumaraswamy, Freeman, & Singh, 2009;

Muthukumaraswamy, Edden, Jones, Swettenham, & Singh, 2009). Therefore currently, it seems that little can be learnt about E/I balance by measuring gamma power in ASD.

An additional metric of gamma band activity is peak induced gamma frequency. Peak gamma frequency has been more precisely linked to E/I balance than gamma power via computational modelling work (Brunel et al., 2014). For instance, higher levels of inhibition have been shown to lead to a higher peak gamma frequency (Brunel et al., 2014). Peak gamma frequency has been shown to be stable over time, and also to be highly heritable (van Pelt, Boomsma, & Fries, 2012), therefore peak gamma frequency may represent a more useful way to investigate E/I balance in human participants. Some studies have shown that visually-induced peak gamma frequency is correlated with resting GABA levels in occipital cortex (Edden et al., 2009; Gaetz, Edgar, Wang, & Roberts, 2011; Muthukumaraswamy et al., 2009) although others have failed to replicate this relationship (Cousijn et al., 2014; Saxena et al., 2013). The technical difficulty in measuring GABA concentration in vivo with MRS and the different scan parameters used in these studies may contribute to the lack of convergence in results, Nevertheless, peak gamma frequency elicited by visual stimuli has been found to be higher in ASD (Dickinson et al., 2016), and correlated with autistic traits in the neurotypical population (Dickinson, Bruyns-Haylett, Jones, & Milne, 2015). In light of previous literature (Edden et al., 2009; Muthukumaraswamy et al., 2009) this suggests that inhibition is increased in participants with ASD. As described below, orientation discrimination thresholds were also found to be decreased in the same cohort of participants with ASD, which concurs with the suggestion that inhibition is increased in these participants.

Taken together therefore, results arising from studying gamma band activity in ASD are inconclusive with regard to E/I balance. One difficulty is that it is not clear exactly how increases or decreases in gamma power should be interpreted with regards to E/I balance, nor is it clear to what extent gamma power is altered in ASD. Gamma frequency, as opposed to gamma power, represents a potentially more fruitful avenue to investigate E/I balance, although to date only one study has measured differences in peak gamma frequency between those with and without ASD.

Table 5. Studies of high frequency neural oscillations in ASD.

Study (Year)	Participants Group: N (mean age in years)	Measure	Finding	Interpretation regarding E/I balance in ASD.[a]
Baruth et al (2010)	ASD: 25 (13.8) NT: 20 (15.3)	Evoked gamma activity elicited by Kanisza figures measured over frontal and parietal areas (EEG).	Decreased power in ASD (30-45Hz).	Decreased inhibition.
Brown et al. (2005)	ASD: 6 (14.7) LD: 8 (14)	Induced gamma activity elicited by Kanisza figures measured over parietal areas (EEG).	Increased induced gamma power (29.3 – 41.5Hz) in ASD.	Increased inhibition.
Buard et al. (2013)	ASD: 12 (28.3) NT: 35 (34.2)	Evoked gamma power elicited by picture naming measured in superior temporal gyrus and inferior frontal gyrus (MEG).	Decreased power in ASD (35-120Hz).	Decreased inhibition.
Cornew et al. (2012)	ASD: 27 (9.8) NT: 21 (10.8)	Spontaneous gamma activity measured over parietal, temporal and occipital areas (EEG).	Increased absolute gamma power (30-120Hz) in ASD.	Increased inhibition.
Dickinson et al. (2016)	ASD: 28 (30.11) NT: 39 (28.77)	Induced gamma activity elicited by square wave grating measured over occipital areas (EEG).	Increased induced peak gamma frequency (30-90Hz) in ASD.	Increased inhibition.
Edgar et al. (2015)	ASD: 105 (10.07) NT: 36 (10.9)	Spontaneous gamma activity measured over superior temporal gyrus (MEG).	Increased absolute gamma power in ASD (20-80Hz)	Increased inhibition.
Edgar et al. (2015)	ASD: 105 (10.07) NT: 36 (10.9)	Evoked gamma activity elicited by pure tones measured over superior temporal gyrus (MEG).	Decreased evoked gamma power in ASD (40Hz)	Decreased inhibition.
Gandal et al. (2010)	ASD: 25 (10.2) NT: 17 (10.8)	Evoked and induced gamma activity elicited by pure tones measured over superior temporal gyrus (MEG).	No group differences (30-50Hz).	No difference.

Gross et al. (2012)	ASD: 10 (14.1) NT:11 (14.8)	Induced activity elicited by faces measured over parietal areas (EEG).	Decreased induced gamma power in ASD (35-45Hz).	Decreased inhibition.
Machado et al. (2013)	ASD: 11 (5.9) NT: 14 (5.6)	Spontaneous gamma activity measured over midline, frontal, temporal, parietal and occipital areas (EEG).	Increased absolute & relative gamma band power (22-55Hz) in ASD.	Increased inhibition.
Maxwell et al. (2013)	ASD: 15 (15.1) NT: 18 (14.2)	Spontaneous gamma activity measured over lateral, central, frontal and parieto-occipital areas (EEG).	Decreased absolute gamma power (30-50Hz) in right lateral electrodes in ASD.	Decreased inhibition.
Milne et al. (2009)	ASD: 20 (12.2) NT: 20 (13.4)	Evoked gamma activity elicited by Gabor patches measured over occipital areas (EEG).	No group difference in evoked gamma power (30-40Hz).	No difference.
Orekhova et al. (2008)	ASD: 21 (5.9) NT: 21 (5.9)	Spontaneous gamma activity measured over frontal, parietal and central areas (EEG).	Increased absolute gamma power (24.4-44Hz) in ASD.	Increased inhibition.
Rojas et al. (2008)	ASD: 11 (31.5) NT: 16 (43.1) Parents of children with ASD: 16 (42.6)	Induced gamma activity elicited by pure tones measured over auditory cortex (MEG).	Increased induced power (40Hz) in ASD and parent group.	Increased inhibition.
Rojas et al. (2008)	ASD: 11 (31.5) NT: 16 (43.1) Parents of children with ASD: 16 (42.6)	Evoked gamma activity elicited by pure tones measured over auditory cortex (MEG).	Decreased evoked gamma power (40Hz) in ASD.	Decreased inhibition.
Snijders et al. (2013)	ASD: 12 (22) NT: 12 (22)	Evoked gamma activity elicited by Gabor patches measured over occipito-parietal areas (EEG).	Decreased evoked power in ASD (60Hz steady state response).	Decreased inhibition.
Sokhadze et al. (2009)	ASD: 13 (17.2) NT: 13 (18.6)	Induced gamma activity elicited by Kanisza figures measured over frontal areas (EEG).	Increased induced power (30-80Hz) in ASD.	Increased inhibition.

Stroganova et al. (2012)	ASD: 23 (5) NT: 23 (5.11)	Evoked gamma activity elicited by Kanisza square measured over occipital areas (EEG).	Decreased gamma power (25-48Hz) in ASD.	Decreased inhibition.
Sun et al. (2012)	ASD: 13 (30.3) NT: 16 (29.7)	Evoked activity elicited by Mooney faces measured over occipito-parietal areas (MEG).	Decreased evoked gamma band power in ASD (in response to upright rather than inverted faces). (25-120Hz)	Decreased inhibition.
Sun et al. (2012)	ASD: 13 (30.3) NT: 16 (29.7)	Induced activity elicited by Mooney faces measured over occipito-parietal areas (MEG).	Decreased in ASD (60-120Hz).	Decreased inhibition.
Sun et al. (2012)	ASD: 13 (30.3) NT: 16 (29.7)	Evoked activity elicited by Mooney faces measured over fronto-central areas (MEG).	Increased (25-60Hz) in ASD.	Increased inhibition.
Sun et al. (2012)	ASD: 13 (30.3) NT: 16 (29.7)	Evoked activity elicited by Mooney faces measured over fronto-central areas (MEG).	Decreased (60-120Hz) in ASD.	Decreased inhibition.
van Diessen et al. (2015)	ASD: 19 (10.6) NT: 19 (10.1)	Spontaneous gamma activity measured over frontal, parietal and temporal areas (EEG).	Increased relative gamma power (30-45Hz) in ASD.	Increased inhibition.
Wilson et al. (2007)	ASD: 10 (12.4) NT: 10 (12)	Evoked gamma activity elicited by auditory clicks measured over left auditory cortex (MEG).	Decreased evoked gamma power (40Hz) in ASD.	Decreased inhibition.
Wright et al. (2012)	ASD: 13 (15.1) NT: 13 (15.7)	Induced gamma activity elicited by faces measured over occipital areas (MEG).	Decreased induced gamma activity in ASD (30-80Hz).	Decreased inhibition.
Wright et al. (2012)	ASD: 13 (15.1) NT: 13 (15.7)	Evoked gamma activity elicited by faces measured over occipital areas (MEG).	No group differences in evoked activity (30-80Hz).	No difference.

NT neurotypical; LD learning difficulties.

[a] Results are interpreted in line with increased gamma activity indicating increased inhibition (e.g. Cardin et al., 2009). However, see the text for a more in depth discussion regarding how E/I balance is reflected by gamma activity.

2.6 Perception

Within the visual psychophysics literature, a substantial body of work suggests a link between perception and excitatory and / or inhibitory neurotransmission. Given this association, some authors have suggested that measuring aspects of perception in ASD may provide a marker for measuring E/I balance in the autistic brain (Freyberg, Robertson, & Baron-Cohen, 2015). As described below (see table 6 for a summary), phenomena that are most directly linked to E/I balance include binocular rivalry, spatial suppression / gain control, and orientation discrimination. However, as with the EEG / MEG data described above, these data provide only indirect evidence for E/I imbalance in ASD, and, collectively, do not converge on a clear direction for any such imbalance.

2.6.1 Binocular Rivalry

Binocular rivalry is a perceptual phenomenon which occurs when a different image is presented to each eye simultaneously. Rather than perceive a stable superimposition of the two images, the participant randomly perceives each image separately for a few moments although combinations of the two images may be perceived during transitions between the two percepts (Wheatstone, 1850). Computational models have shown that changes to E/I balance could lead to alterations in rivalry dynamics including: the rate of switches between two percepts; how long an individual percept is experienced; how long a mixed percept is experienced; and / or the length of the transition period between the two images (travelling wave speed; Laing and Chow, 2002; Said and Heeger, 2013; Seely and Chow, 2011; Wilson et al., 2001). For example, modelling work has shown that a higher level of excitation would lead to faster rivalry dynamics, due to faster travelling waves (Wilson et al., 2001). This is supported by the finding that administration of lorazepam (a GABA agonist) decreases the rate of perceptual switches suggesting that higher levels of inhibition lead to slower rivalry dynamics (van Loon, Knapen, Scholte, & John-Saaltink, 2013).

To our knowledge, four studies have measured binocular rivalry in individuals with ASD. Three of these studies have found significant differences in binocular rivalry in ASD compared to neurotypical individuals (Freyberg et al., 2015; Robertson, Kravitz, Freyberg, Baron-Cohen, & Baker, 2013; Robertson et al., 2015), and one study found no differences (Said, Egan, Minshew, Behrmann, & Heeger, 2013). Where differences

between individuals with and without ASD have been found, data concur to suggest 'slower' binocular rivalry in ASD, which is characterised by a reduced switching rate due to a longer time perceiving mixed percepts (Freyberg et al., 2015; Robertson et al., 2013, 2015). Robertson and colleagues (2015) report that there is a decreased rate of perceptual suppression in ASD, which manifests as a larger amount of time perceiving a mixed percept, and less time perceiving an individual percept. When considered alongside their finding that occipital GABA level is correlated with perceptual suppression in neurotypical participants, this would indicate that decreased levels of occipital GABA may be present in ASD. However, individual differences in occipital GABA levels did not correlate with perceptual suppression in participants with ASD. Furthermore, there were no differences in occipital GABA levels between the participants with and without ASD, despite finding differences in binocular rivalry (Robertson et al. 2015). Robertson and colleagues conclude from these data that an aspect of GABA functioning, which is not captured by MRS, is atypical in ASD, and that this leads to the observed differences in binocular rivalry. However, it is unclear from these data what such an unobserved difference may be. Taken together, slower perceptual rivalry in ASD may suggest atypical E/I balance in ASD, but it is not entirely clear whether this finding reflects increased or decreased excitation relative to inhibition.

2.6.2 Spatial suppression and gain control

Spatial suppression refers to the fact that an increase in stimulus size can lead to a decrease in how easily stimuli are perceived (Tadin et al., 2003). The phenomenon relies on centre surround suppression, meaning that decreased inhibition would lead to weaker spatial suppression, and a reduced effect of increasing stimulus size on perception (Golomb et al., 2009). Foss-Feig et al. (2013) investigated spatial suppression in individuals with and without ASD using a motion discrimination paradigm in which participants were asked to indicate the direction of drifting gratings that varied in size and contrast. It was predicted that if inhibitory mechanisms are altered in ASD, differences in spatial suppression would be seen between the participants with and without ASD. However, spatial suppression was found to be unaltered in ASD. There was however an interesting effect of stimulus contrast in this study, as although participants with ASD showed similar results to controls for low contrast stimuli, they performed systematically better than controls when stimuli were presented at high contrast (regardless of size). It was suggested that this pattern of performance

indicates abnormal gain control in ASD. Like spatial suppression, gain control is thought to reflect an inhibitory mechanism: specifically, the saturation of neural responses at high contrast (Albrecht & Hamilton, 1982). This has been found to be weakened when gabazine (a $GABA_A$ antagonist) is topically applied to the visual cortex of cats (Katzner, Busse, & Carandini, 2011). Therefore, although spatial suppression was unaltered in ASD, the weakening of response gain in ASD may therefore indicate decreased GABA levels, and therefore reduced inhibition in ASD.

2.6.3 Perceptual Discrimination

In contrast to the conclusion made by Foss-Feig et al. (2013), evidence from perceptual discrimination may suggest increased inhibition in ASD. For example, as described below, superior orientation discrimination and superior pitch discrimination have been reported in ASD, both of which are associated with increased inhibitory neurotransmission.

We have recently found that orientation discrimination thresholds are decreased in adults with ASD (Dickinson et al., 2016, although see Schwarzkopf, Anderson, de Haas, White, & Rees, 2014; Shafai, Armstrong, Iarocci, & Oruc, 2015), and also that orientation discrimination thresholds correlate with autistic traits in the neurotypical population (Dickinson, Jones, & Milne, 2014). Inhibitory mechanisms are implicated in orientation discrimination as they are known to be involved in tuning the orientation selectivity of cells, as orientation selective neurons become narrowly tuned to a particular orientation through lateral inhibition (Hubel & Wiesel, 1968), and GABAergic inhibition has been shown to directly influence orientation discrimination ability. For example, topical application of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) to neurons in the primary visual cortex of anaesthetised cats leads to orientation selective cells becoming more narrowly tuned, and increases their orientation selectivity (Li et al., 2008). Conversely, the application of GABA antagonists reduces the orientation selectivity of cells in primary visual cortex (Katzner et al., 2011; Sillito, 1975). Resting levels of GABA in the occipital cortex are also inversely correlated with orientation discrimination thresholds in neurotypical human observers (Edden, Muthukumaraswamy, Freeman, & Singh, 2009) suggesting that GABA mediated inhibition plays a major role in establishing the sharp orientation tuning of neurons, and leads to enhanced orientation

discrimination. Therefore our finding of enhanced orientation discrimination in ASD is consistent with inhibition being increased rather than decreased in ASD.

Other aspects of perceptual discrimination, such as hue discrimination, are impaired, rather than enhanced in ASD (Franklin et al., 2010; Franklin, Sowden, Burley, Notman, & Alder, 2008; Heaton, Ludlow, & Roberson, 2008). Although, again, this is in-line with the suggestion of increased inhibition given that medication which increases GABA levels, such as vigabatrin, has been shown to lead to colour perception impairments in healthy individuals (Mecarelli, Rinalduzzi, & Accornero, 2001). In the auditory domain, pitch discrimination is enhanced in ASD (Bonnel et al., 2003, 2010; Heaton, Hudry, Ludlow, & Hill, 2008; Jones et al., 2009; Meilleur, Berthiaume, Bertone, & Mottron, 2014; O'Riordan & Passetti, 2006; Stanutz, Wapnick, & Burack, 2014). Similar to orientation discrimination, pitch discrimination is mediated by lateral inhibition (Houtgast, 1972), as auditory cortex cells also become more narrowly tuned to particular frequencies through inhibition (Wang, Caspary, & Salvi, 2000; Wang, Ding, & Salvi, 2002), suggesting increased inhibition in ASD However, some studies find that enhanced pitch discrimination occurs only in a subgroup of individuals with ASD (Bonnel et al., 2010; Jones et al., 2009). Taken together with studies that find orientation discrimination to be unaltered in ASD (Schwarzkopf, Anderson, de Haas, White, & Rees, 2014; Shafai, Armstrong, Iarocci, & Oruc, 2015) this may suggest that superior perceptual discrimination, and increased inhibition, occurs only in a sub-group of individuals with ASD.

Table 6. Studies employing perceptual measures which can be used to infer E/I balance in ASD.

Study (Year)	Participants Group: N (mean age in years)	Measure	Finding	Interpretation regarding E/I balance in ASD.
Bonnel et al. (2003)	ASD: 12 (17.91) NT: 12 (16.58)	Pitch discrimination.	Superior pure tone pitch discrimination in ASD.	Increased inhibition.
Bonnel et al. (2010)	ASD:15 (24.16) Asperger's syndrome:14 (22.71) NT:15 (21.40)	Pitch discrimination.	Superior pure tone pitch discrimination in ASD. No difference in Asperger's syndrome.	Increased inhibition.
Dickinson et al. (2016)	ASD: 28 (30.11) NT: 39 (28.77)	Orientation discrimination.	Enhanced orientation discrimination in ASD.	Increased inhibition.
Foss-Feig et al. (2013)	Low contrast stimuli ASD: 10 (11.4) NT: 13 (10.7) High contrast stimuli ASD: 15 (12.7) NT: 17 (12.4)	Spatial suppression (motion discrimination paradigm with high and low contrast stimuli).	No group differences in spatial suppression. However, weaker response gain control.	Decreased inhibition.
Franklin et al. (2008)	ASD: 19 (10.9) NT: 14 (9.8)	Colour discrimination.	Impaired colour discrimination in ASD.	Increased inhibition.
Franklin et al. (2010)	ASD: 14 (13.71) NT: 14 (13.93)	Colour discrimination.	Impaired colour discrimination in ASD.	Increased inhibition.
Franklin et al. (2010)	ASD: 34 (12.74) NT: 33 (12.48)	Colour discrimination.	Impaired colour discrimination in ASD.	Increased inhibition.
Freyberg et al. (2015)	ASD: 26 (32) NT: 27 (28.7)	Binocular rivalry.	Reduced switch rate due to longer mixed percepts.	Increased excitation.
Heaton et al. (2008)	ASD: 14 (10.5) NT & LD: 14 (10.5)	Pitch discrimination.	Superior pitch discrimination in ASD.	Increased inhibition.
Heaton et al. (2008)	ASD:13 (11.4) LD: 13 (11.5) NT: 13 (11)	Colour discrimination.	Impaired colour discrimination in ASD.	Increased inhibition.
Jones et al. (2009)	ASD: 72 (15.5) NT: 48 (15.5)	Auditory discrimination.	No group differences. 20% of individuals with	No difference.

			ASD showed superior auditory discrimination (frequency).	
Meilleur et al. (2014)	ASD: 34 (NR) NT: 33 (NR)	Pitch discrimination.	Superior pure tone pitch discrimination in ASD	Increased inhibition.
O'Riordan & Passetti (2006)	ASD: 12 (8.58) NT: 12 (8.58)	Pitch discrimination.	Superior pitch discrimination in ASD.	Increased inhibition.
Robertson et al. (2015)	ASD: 20 (29.61) NT: 21 (29.1)	Binocular rivalry.	Decreased switch rate due to longer mixed percepts.	Increased excitation.
Robertson et al. (2013)	ASD: 20 (33.3) NT: 19 (28.79)	Binocular rivalry.	Decreased switch rate due to longer mixed percepts.	Increased excitation.
Said et al. (2013)	ASD: 19 (24) NT: 20 (25)	Binocular rivalry.	No group differences.	No difference.
Schwarzkopf et al. (2014)	ASD: 15 (37.5) NT: 12 (35.1)	Orientation discrimination.	No group differences.	No difference.
Shafai et al. (2015)	ASD: 29 (23.2) NT: 29 (26.3)	Orientation discrimination.	No group differences.	No difference.
Stanutz et al. (2014)	ASD: 25 (10.6) NT: 25 (10.41)	Pitch discrimination.	Superior pitch discrimination in ASD.	Increased inhibition.

NT neurotypical.

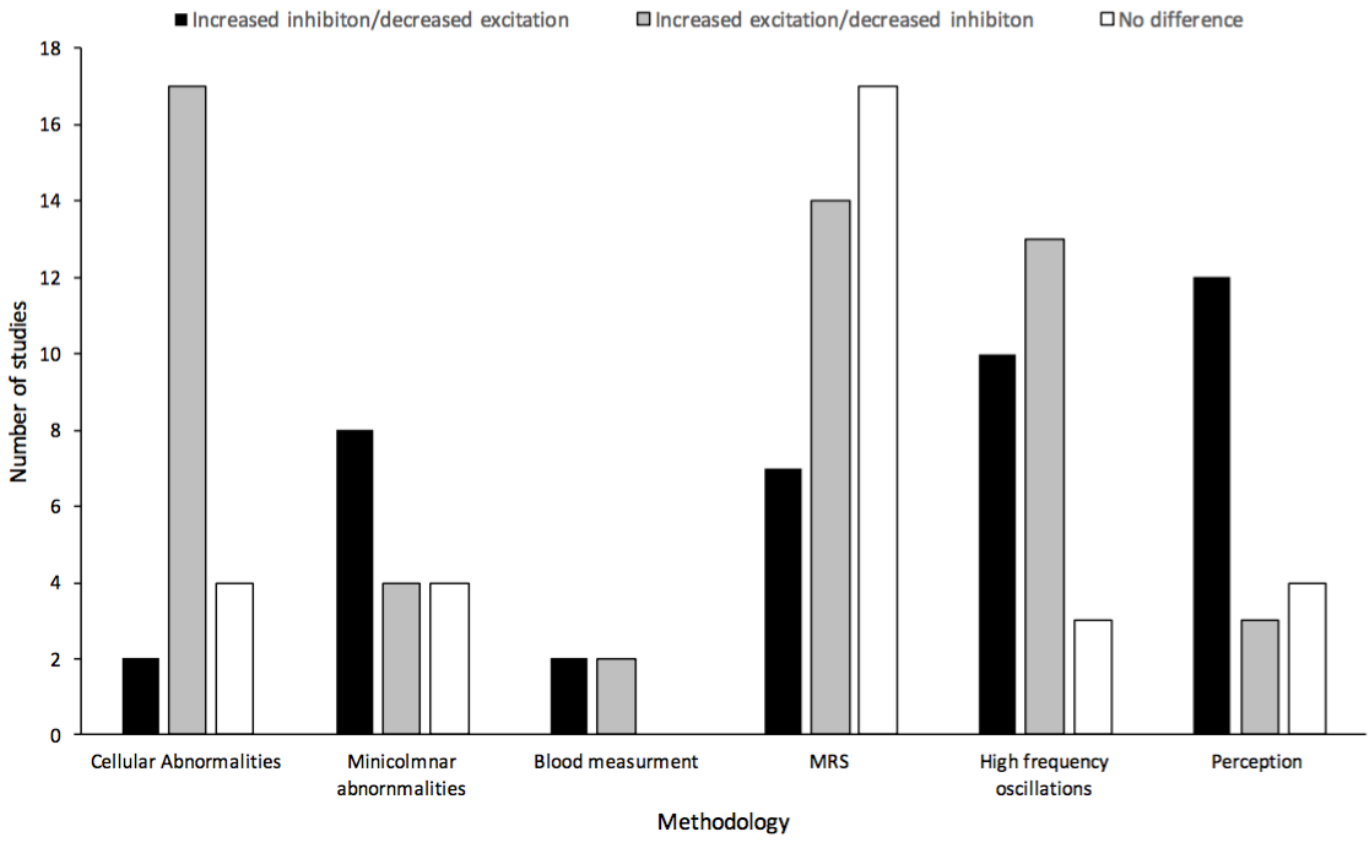

Figure 1. The number of findings from studies in each section of this review which support either a net increase in inhibition, a net increase in excitation, or no difference in E/I balance.

3. Conclusion

Alteration of E/I balance has been suggested as a possible neural mechanism underlying the symptoms of ASD. As this review demonstrates, there is much evidence to suggest that excitatory and inhibitory neurotransmission is altered in ASD. However, results do not concur with respect to the direction of E/I imbalance in ASD. This is illustrated in figure 1, which demonstrates the number of findings from studies in

each section of this article which concur with either a net increase in inhibition (either through increased inhibition or decreased excitation), a net increase in excitation (either through increased excitation or dressed inhibition), or no difference in E/I balance. A recurring theme in the literature is that despite no unequivocal demonstration that either inhibition or excitation is increased in ASD, there appears to be an a priori assumption in many papers that there is clear existing evidence for increased excitation in ASD. Consequently many new research findings are interpreted in this context, without due consideration of the assumptions underlying linking certain techniques to measuring E/I balance.

Three further important points arise from this review. Firstly, each of the methods used to measure or infer E/I balance in ASD has a number of limitations and can provide only one small piece of evidence in a very large puzzle. Secondly, it is possible that E/I balance is altered in different ways in different areas of the brain in ASD, and thirdly, it is possible that there are different sub-types of ASD that have different neural profiles with respect to E/I balance.

Given the inherent difficulty in measuring E/I balance in vivo, a valuable way forward would be to utilise multiple methodologies within the same study. For instance, obtaining multiple data points from individual participants may strengthen conclusions by finding converging results. To date two studies, described above, have taken this approach. Robertson et al (2016) measured binocular rivalry and also occipital GABA levels in ASD. In this study, slower binocular rivalry indicated disruption to E/I balance in ASD, although no group differences were found in occipital GABA levels. Dickinson et al. (2016) found a significant difference between orientation discrimination thresholds and peak gamma frequency in ASD, concluding that both variables pointed towards increased inhibition in ASD. Future studies could be much more ambitious in this regard, and it is hoped that future researchers will be able to obtain data from multiple methodologies from the same individual in order to more clearly identify the way in which E/I balance is altered in ASD (if at all). For example, a multi-technique study which examines sensory discrimination thresholds within different modalities (such as pitch discrimination and orientation discrimination) as well as measuring neurotransmitter levels in different sensory cortices would be an effective way to address whether E/I balance is altered in a consistent way across different areas of the cortex.

To conclude, we have provided an overview of data emerging from a range of techniques that purport to measure E/I balance in ASD. While there is clear evidence that disruption to E/I balance is implicated in ASD, the direction of any such imbalance is less clear. Crucially, this may be important in understanding the variability seen in response to clinical trials of drugs that attempt to modulate E/I balance in ASD (Erickson et al., 2014). The data reviewed here highlight the importance of ambitious future research, which will obtain data from a range of different methodologies from large samples of participants. As far as we can see, this will be the most effective way to reveal the true landscape of E/I imbalance in ASD.

References

Albrecht, D. G., & Hamilton, D. B. (1982). Striate cortex of monkey and cat: contrast response function. *Journal of neurophysiology*, *48*(1), 217–237.

Balz, J., Keil, J., Roa Romero, Y., Mekle, R., Schubert, F., Aydin, S., Ittermann, B., et al. (2016). GABA concentration in superior temporal sulcus predicts gamma power and perception in the sound-induced flash illusion. *NeuroImage*, *125*, 724–730.

Bartos, M., Vida, I., & Jonas, P. (2007). Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nature reviews. Neuroscience*, *8*(1), 45–56.

Baruth, J. M., Casanova, M. F., El-Baz, A., Horrell, T., Mathai, G., Sears, L., & Sokhadze, E. (2010). Low-frequency repetitive transcranial magnetic stimulation modulates evoked-gamma frequency oscillations in autism spectrum disorder. *Journal of neurotherapy*, *14*(3), 179-194.

Bejjani, A., O'Neill, J., Kim, J. A., Frew, A. J., Yee, V. W., Ly, R., Kitchen, C., et al. (2012). Elevated glutamatergic compounds in pregenual anterior cingulate in pediatric autism spectrum disorder demonstrated by1H MRS and 1H MRSI. *PLoS ONE*, *7*(7).

Bernardi, S., Anagnostou, E., Shen, J., Kolevzon, A., Buxbaum, J. D., Hollander, E., Hof, P. R., et al. (2011).

In vivo 1H-magnetic resonance spectroscopy study of the attentional networks in autism. *Brain Research*, *1380*, 198–205.

Bertone, A., Mottron, L., Jelenic, P., & Faubert, J. (2005). Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain*, *128*(10), 2430–2441.

Blatt, G. J., Fitzgerald, C. M., Guptill, J. T., Booker, A. B., Kemper, T. L., & Bauman, M. L. (2001). Density and distribution of hippocampal neurotransmitter receptors in autism: an autoradiographic study. *Journal of autism and developmental disorders*, *31*(6), 537-543.

Blundell, J., Blaiss, C. A., Etherton, M. R., Espinosa, F., Tabuchi, K., Walz, C., Bolliger, M. F., et al. (2010). Neuroligin-1 deletion results in impaired spatial memory and increased repetitive behavior. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *30*(6), 2115–29.

Bonnel, A., McAdams, S., Smith, B., Berthiaume, C., Bertone, A., Ciocca, V., Burack, J. A., et al. (2010). Enhanced pure-tone pitch discrimination among persons with autism but not Asperger syndrome. *Neuropsychologia*, *48*(9), 2465–2475.

Bonnel, A., Mottron, L., Peretz, I., Trudel, M., Gallun, E., & Bonnel, A.-M. (2003). Enhanced pitch sensitivity in individuals with autism: a signal detection analysis. *Journal of cognitive neuroscience*, *15*(2), 226–235.

Brix, M. K., Ersland, L., Hugdahl, K., Grüner, R., Posserud, M.-B., Hammar, Å., Craven, A. R., et al. (2015). "Brain MR spectroscopy in autism spectrum disorder—the GABA excitatory/inhibitory imbalance theory revisited." *Frontiers in Human Neuroscience*, *9*, 1–12.

Brown, C., Gruber, T., Boucher, J., Rippon, G., & Brock, J. (2005). Gamma abnormalities during perception of illusory figures in autism. *Cortex*, *41*(3), 364–376.

Brown, M. S., Singel, D., Hepburn, S., & Rojas, D. C. (2013). Increased Glutamate Concentration in the Auditory Cortex of Persons With Autism and First-Degree Relatives: A 1H-MRS Study. *Autism Research*, *6*(1), 1-10.

Brunel, N., & Wang, X. J. (2003). What determines the frequency of fast network oscillations with irregular neural discharges? I. Synaptic dynamics and excitation-inhibition balance. *Journal of*

neurophysiology, *90*(1), 415-430.

Bryson, S. E., Clark, B. S., & Smith, I. M. (1988). First report of a Canadian epidemiological study of autistic syndromes. *Journal of Child Psychology and Psychiatry*, *29*(4), 433-445.

Buard, I., Rogers, S. J., Hepburn, S., Kronberg, E., & Rojas, D. (2013). Altered oscillation patterns and connectivity during picture naming in autism. *Frontiers in human neuroscience, 7*, 742.

Buxhoeveden, D. P., Semendeferi, K., Buckwalter, J., Schenker, N., Switzer, R., & Courchesne, E. (2007). Reduced minicolumns in the frontal cortex of patients with autism. *Neuropathology and Applied Neurobiology*, *33*(5), 597.

Canitano, R. (2007). Epilepsy in autism spectrum disorders. *Eur.Child Adolesc.Psychiatry*, *16*(1), 61–66.

Cardin, J. A., Carlén, M., Meletis, K., Knoblich, U., Zhang, F., Deisseroth, K., Tsai, L.-H., et al. (2009). Driving fast-spiking cells induces gamma rhythm and controls sensory responses. *Nature*, *459*(7247), 663–667.

Casanova, M. F., Buxhoeveden, D. P., Switala, A. E., & Roy, E. (2002a). Asperger's syndrome and cortical neuropathology. *J Child Neurol*, *17*(2), 142–145.

Casanova, M. F., Buxhoeveden, D. P., Switala, A. E., & Roy, E. (2002b). Minicolumnar pathology in autism. *Neurology*, *58*, 428–432.

Casanova, M. F., Buxhoeveden, D., & Gomez, J. (2003). Disruption in the Inhibitory Architecture of the Cell Minicolumn: Implications for Autisim. *The Neuroscientist*, *9*(6), 496–507.

Casanova, M. F., van Kooten, I. A. J., Switala, A. E., van Engeland, H., Heinsen, H., Steinbusch, H. W. M., Hof, P. R., et al. (2006). Minicolumnar abnormalities in autism. *Acta Neuropathologica*, *112*(3), 287–303.

Chez, M. G., Chang, M., Krasne, V., Coughlan, C., Kominsky, M., & Schwartz, A. (2006). Frequency of epileptiform EEG abnormalities in a sequential screening of autistic patients with no known clinical epilepsy from 1996 to 2005. *Epilepsy and Behavior*, *8*(1), 267–271.

Christensen, D. L. (2016). Prevalence and characteristics of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2012. *MMWR. Surveillance Summaries*, *65*.

Cochran, D. M., Sikoglu, E. M., Hodge, S. M., Edden, R. A., Foley, A., Kennedy, D. N., ... & Frazier, J. A. (2015). Relationship among glutamine, γ-aminobutyric acid, and social cognition in autism spectrum disorders. *Journal of child and adolescent psychopharmacology*, *25*(4), 314-322.

Coghlan, S., Horder, J., Inkster, B., Mendez, M. A., Murphy, D. G., & Nutt, D. J. (2012). GABA system dysfunction in autism and related disorders: from synapse to symptoms. *Neuroscience and biobehavioral reviews*, *36*(9), 2044–55.

Cornew, L., Roberts, T. P., Blaskey, L., & Edgar, J. C. (2012). Resting-state oscillatory activity in autism spectrum disorders. *J Autism Dev Disord*, *42*(9), 1884–1894.

Corrigan, N. M., Shaw, D. W. W., Estes, A. M., Richards, T. L., Munson, J., Friedman, S. D., Dawson, G., et al. (2013). Atypical developmental patterns of brain chemistry in children with autism spectrum disorder. *JAMA psychiatry*, *70*(9), 964–74.

Cousijn, H., Haegens, S., Wallis, G., Near, J., Stokes, M. G., Harrison, P. J., & Nobre, A. C. (2014). Resting GABA and glutamate concentrations do not predict visual gamma frequency or amplitude. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(25), 9301–6.

de Felipe, J. (1999). Chandelier cells and their possible implication in epilepsy. *Neurologia*, *14 Suppl 3*, 7–19.

DeVito, T. J., Drost, D. J., Neufeld, R. W., Rajakumar, N., Pavlosky, W., Williamson, P., & Nicolson, R. (2007). Evidence for cortical dysfunction in autism: a proton magnetic resonance spectroscopic imaging study. *Biological psychiatry*, *61*(4), 465-473.

Dhossche, D., Applegate, H., Abraham, A., Maertens, P., Bland, L., Bencsath, A., & Martinez, J. (2002). Elevated plasma gamma-aminobutyric acid (GABA) levels in autistic youngsters: stimulus for a GABA hypothesis of autism. *Medical science monitor : international medical journal of experimental and clinical research*, *8*(8), PR1–R6.

Dickinson, A., Bruyns-Haylett, M., Jones, M., & Milne, E. (2015). Increased peak gamma frequency in individuals with higher levels of autistic traits. *European Journal of Neuroscience*, *41*(8), 1095–1101.

Dickinson, A., Bruyns-Haylett, M., Smith, R., Jones, M., & Milne, E. (2016). Superior orientation

discrimination and increased peak gamma frequency in autism spectrum conditions. *Journal of abnormal psychology*, *125*(3), 412.

Dickinson, A., Jones, M., & Milne, E. (2014). Oblique orientation discrimination thresholds are superior in those with a high level of autistic traits. *Journal of Autism and Developmental Disorders*, *44*(11), 2844–2850.

Doyle-Thomas, K. A. R., Card, D., Soorya, L. V., Ting Wang, A., Fan, J., & Anagnostou, E. (2014). Metabolic mapping of deep brain structures and associations with symptomatology in autism spectrum disorders. *Research in Autism Spectrum Disorders*, *8*(1), 44–51.

DSM-5 American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders. *Arlington: American Psychiatric Publishing*.

Edden, R. A. E., Muthukumaraswamy, S. D., Freeman, T. C. A., & Singh, K. D. (2009). Orientation Discrimination Performance Is Predicted by GABA Concentration and Gamma Oscillation Frequency in Human Primary Visual Cortex. *Journal of Neuroscience*, *29*(50), 15721–15726.

Edden, R. A. E., Muthukumaraswamy, S. D., Freeman, T. C. A., & Singh, K. D. (2009). Orientation discrimination performance is predicted by GABA concentration and gamma oscillation frequency in human primary visual cortex. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *29*(50), 15721–15726.

Edgar, J. C., Heiken, K., Chen, Y. H., Herrington, J. D., Chow, V., Liu, S., ... & Qasmieh, S. (2015). Resting-state alpha in autism spectrum disorder and alpha associations with thalamic volume. *Journal of autism and developmental disorders*, *45*(3), 795-804.

Engel, J. J. (1996). Excitation and inhibition in epilepsy. *The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques*, *23*(3), 167–74.

Epperson, C. N., Haga, K., Mason, G. F., Sellers, E., Gueorguieva, R., Zhang, W., Weiss, E., et al. (2002). Cortical γ-Aminobutyric Acid Levels Across the Menstrual Cycle in Healthy Women and Those With Premenstrual Dysphoric Disorder. *Archives of General Psychiatry*, *59*(9), 851.

Erickson, C. A., Veenstra-Vanderweele, J. M., Melmed, R. D., McCracken, J. T., Ginsberg, L. D., Sikich, L., Scahill, L., et al. (2014). STX209 (Arbaclofen) for autism spectrum disorders: An 8-week open-

label study. *Journal of Autism and Developmental Disorders*, *44*(4), 958–964.

Fatemi, S. H., Halt, A. R., Stary, J. M., Kanodia, R., Schulz, S. C., & Realmuto, G. R. (2002). Glutamic acid decarboxylase 65 and 67 kDa proteins are reduced in autistic parietal and cerebellar cortices. *Biological Psychiatry*, *52*(8), 805–810.

Fatemi, S. H., Reutiman, T. J., Folsom, T. D., Rustan, O. G., Rooney, R. J., & Thuras, P. D. (2014). Downregulation of GABAA receptor protein subunits α6, β2, δ, ε, γ2, θ, and ρ2 in superior frontal cortex of subjects with autism. *Journal of autism and developmental disorders*, *44*(8), 1833-1845.

Fatemi, S., Folsom, T., Reutiman, T., & Thuras, P. (2009). Expression of GABAB Receptors Is Altered in Brains of Subjects with Autism. *Cerebellum*, *8*(1), 64–69.

Fatemi, S., Reutiman, T., Folsom, T., & Thuras, P. (2009). GABAA receptor downregulation in brains of subjects with autism. *Journal of Autism and Developmental Disorders*, *39*(2), 223–230.

Favorov, O. V, & Kelly, D. G. (1994). Minicolumnar organization within somatosensory cortical segregates. 1. Development of affererent connections. *Cerebral Cortex*, *4*(4), 408–427.

Foss-Feig, J. H., Tadin, D., Schauder, K. B., & Cascio, C. J. (2013). A Substantial and Unexpected Enhancement of Motion Perception in Autism. *Journal of Neuroscience*, *33*(19), 8243–8249.

Franklin, A., Sowden, P., Burley, R., Notman, L., & Alder, E. (2008). Color perception in children with autism. *Journal of autism and developmental disorders*, *38*(10), 1837-1847.

Franklin, A., Sowden, P., Notman, L., Gonzalez-Dixon, M., West, D., Alexander, I., Loveday, S., et al. (2010). Reduced chromatic discrimination in children with autism spectrum disorders. *Developmental Science*, *13*(1), 188–200.

Freyberg, J., Robertson, C., & Baron-Cohen, S. (2015). Atypical Binocular Rivalry Dynamics of Simple and Complex Stimuli in Autism. *Journal of vision*,*15*(12), 643-643.

GABAA receptor downregulation in brains of subjects with autism. (2009). *Journal of Autism and Developmental Disorders*, *39*(2), 223–230.

Gaetz, W., Bloy, L., Wang, D. J., Port, R. G., Blaskey, L., Levy, S. E., & Roberts, T. P. L. (2014). GABA estimation in the brains of children on the autism spectrum: Measurement precision and regional cortical variation. *NeuroImage*.

Gaetz, W., Edgar, J. C., Wang, D. J., & Roberts, T. P. L. (2011). Relating MEG measured motor cortical oscillations to resting gamma-Aminobutyric acid (GABA) concentration. *NeuroImage*, *55*(2), 616–621.

Galambos, R., Basar, E., & Bullock, T. H. (1992). A comparison of certain gamma band (40-Hz) brain rhythms in cat and man. *Induced Rhythms in the Brain*, 201–216.

Gandal, M. J., Edgar, J. C., Ehrlichman, R. S., Mehta, M., Roberts, T. P. L., & Siegel, S. J. (2010). Validating gamma oscillations and delayed auditory responses as translational biomarkers of autism. *Biological Psychiatry*, *68*(12), 1100–1106.

Gao, F., Edden, R. A., Li, M., Puts, N. A., Wang, G., Liu, C., ... & Wang, X. (2013). Edited magnetic resonance spectroscopy detects an age-related decline in brain GABA levels. *Neuroimage*, *78*, 75-82.

Golomb, J. D., McDavitt, J. R. B., Ruf, B. M., Chen, J. I., Saricicek, A., Maloney, K. H., Hu, J., et al. (2009). Enhanced visual motion perception in major depressive disorder. *Journal of neuroscience , 29*(28), 9072–7.

Gross, E., El-Baz, A. S., Sokhadze, G. E., Sears, L., Casanova, M. F., & Sokhadze, E. M. (2012). Induced EEG gamma oscillation alignment improves differentiation between autism and ADHD group responses in a facial categorization task. *Journal of neurotherapy, 16*(2), 78-91.

Gustafsson, L. (1997a). Excessive lateral feedback synaptic inhibition may cause autistic characteristics. *Journal of Autism & Developmental Disorders*, *27*(2), 219–220.

Gustafsson, L. (1997b). Inadequate cortical feature maps: a neural circuit thory of autism. *Biological Psychiatry*, *3223*(97), 1138–1147.

Haider, B., Häusser, M., & Carandini, M. (2013). Inhibition dominates sensory responses in the awake cortex. *Nature*, *493*(7430), 97–100.

Hardan, A. Y., Minshew, N. J., Melhem, N. M., Srihari, S., Jo, B., Bansal, R., ... & Stanley, J. A. (2008). An MRI and proton spectroscopy study of the thalamus in children with autism. *Psychiatry Research: Neuroimaging*,*163*(2), 97-105.

Hassan, T. H., Abdelrahman, H. M., Fattah, N. R. A., El-Masry, N. M., Hashim, H. M., El-Gerby, K. M., &

Fattah, N. R. A. (2013). Blood and brain glutamate levels in children with autistic disorder. *Research in Autism Spectrum Disorders*, *7*(4), 541-548.

Heaton, P., Hudry, K., Ludlow, A., & Hill, E. (2008). Superior discrimination of speech pitch and its relationship to verbal ability in autism spectrum disorders. *Cognitive neuropsychology*, *25*(6), 771–782.

Heaton, P., Ludlow, A., & Roberson, D. (2008). When less is more: Poor discrimination but good colour memory in autism. *Research in Autism Spectrum Disorders*, *2*(1), 147–156.

Hensch, T. K. (2007). Columnar Architecture Sculpted by GABA Circuits in Developing. *Science*, *1678*(2004).

Horder, J., Lavender, T., Mendez, M. A., O'Gorman, R., Daly, E., Craig, M. C., ... & Murphy, D. G. (2014). Reduced subcortical glutamate/glutamine in adults with autism spectrum disorders: a [1H] MRS study. *Translational psychiatry*,*4*(2), e364.

Houtgast, T. (1972). Psychophysical evidence for lateral inhibition in hearing. *The Journal of the Acoustical Society of America*, *51*(6), 1885–1894.

Hubel, D., & Wiesel, T. (1968). <jphysiol01104-0228.pdf>. *The Journal of physiology*.

Hughes, J. R., & Melyn, M. (2005). EEG and seizures in autistic children and adolescents: further findings with therapeutic implications. *Clinical EEG and neuroscience*, *36*(1), 15–20.

Hussman, J. P. (n.d.). Letters to the Editor: Suppressed GABAergic Inhibition as a Common Factor in Suspected Etiologies of Autism. *Journal of Autism and Developmental Disorders*, *31*(2), 247–248.

Jones, C. R. G., Happé, F., Baird, G., Simonoff, E., Marsden, A. J. S., Tregay, J., Phillips, R. J., et al. (2009). Auditory discrimination and auditory sensory behaviours in autism spectrum disorders. *Neuropsychologia*, *47*(13), 2850–2858.

Joshi, G., Biederman, J., Wozniak, J., Goldin, R. L., Crowley, D., Furtak, S., ... & Gönenç, A. (2013). Magnetic resonance spectroscopy study of the glutamatergic system in adolescent males with high-functioning autistic disorder: a pilot study at 4T. *European archives of psychiatry and clinical neuroscience*, *263*(5), 379-384.

Katzner, S., Busse, L., & Carandini, M. (2011). GABAA Inhibition Controls Response Gain in Visual

Cortex. *Journal of Neuroscience*, *31*(16), 5931–5941.

Laing, C. R., & Chow, C. C. (2002). A spiking neuron model for binocular rivalry. *Journal of computational neuroscience*, *12*(1), 39-53.

Lally, N., Mullins, P. G., Roberts, M. V., Price, D., Gruber, T., & Haenschel, C. (2014). Glutamatergic correlates of gamma-band oscillatory activity during cognition: a concurrent ER-MRS and EEG study. *Neuroimage*, *85*, 823-833.

Levin, A. R., & Nelson, C. A. (2015). Inhibition-based biomarkers for autism spectrum disorder. *Neurotherapeutics*, *12*(3), 546-552.

Lewis, D. A., Cho, R. Y., Carter, C. S., Eklund, K., Forster, S., Kelly, M. A., & Montrose, D. (2008). Subunit-selective modulation of GABA type A receptor neurotransmission and cognition in schizophrenia. *American Journal of Psychiatry*, *165*(12), 1585–1593.

Li, G., Yang, Y., Liang, Z., Xia, J., Yang, Y., & Zhou, Y. (2008). GABA-mediated inhibition correlates with orientation selectivity in primary visual cortex of cat. *Neuroscience*, *155*(3), 914–922.

Machado, C., Estevez, M., Melillo, R., Leisman, G., Carrick, F. R., Machado, A., ... & Carballo, M. (2013). QUANTITATIVE RESTING EEG IN THE AUTISTIC SPECTRUM DISORDER. *International Journal of Child Health and Human Development*, *6*(4), 511.

Markram, H., Rinaldi, T., & Markram, K. (2007). The intense world syndrome--an alternative hypothesis for autism. *Frontiers in neuroscience*, *1*(1), 77–96.

Markram, K., Rinaldi, T., La Mendola, D., Sandi, C., & Markram, H. (2008). Abnormal fear conditioning and amygdala processing in an animal model of autism. *Neuropsychopharmacology*, *33*(4), 901–912.

Maxwell, C. R., Villalobos, M. E., Schultz, R. T., Herpertz-Dahlmann, B., Konrad, K., & Kohls, G. (2015). Atypical laterality of resting gamma oscillations in autism spectrum disorders. *Journal of autism and developmental disorders*, *45*(2), 292-297.

McKavanagh, R., Buckley, E., & Chance, S. A. (2015). Wider minicolumns in autism: A neural basis for altered processing? *Brain*, *138*(7), 2034–2045.

McVicar, K. A., Ballaban-Gil, K., Rapin, I., Moshe, S. L., & Shinnar, S. (2005). Epileptiform EEG

abnormalities in children with language regression.*Neurology*, *65*(1), 129-131.

Mecarelli, O., Rinalduzzi, S., & Accornero, N. (2001). Changes in color vision after a single dose of vigabatrin or carbamazepine in healthy volunteers. *Clin Neuropharmacol*, *24*(1), 23–26.

Meilleur, A. A. S., Berthiaume, C., Bertone, A., & Mottron, L. (2014). Autism-specific covariation in perceptual performances: "g" or "p" Factor? *PLoS ONE*, *9*(8).

Miles, J. H. (2011). Autism spectrum disorders—a genetics review. *Genetics in Medicine*, *13*(4), 278-294.

Milne, E., Scope, A., Pascalis, O., Buckley, D., & Makeig, S. (2009). Independent Component Analysis Reveals Atypical Electroencephalographic Activity During Visual Perception in Individuals with Autism. *Biol Psychiatry*, *65*(1), 22–30.

Mountcastle, V. (1997). The columnar organization of the cerebral cortex. *Brain*, *120*, 701–722.

Muthukumaraswamy, S. D., Edden, R. a E., Jones, D. K., Swettenham, J. B., & Singh, K. D. (2009). Resting GABA concentration predicts peak gamma frequency and fMRI amplitude in response to visual stimulation in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(20), 8356–8361.

O'Riordan, M., & Passetti, F. (2006). Discrimination in autism within different sensory modalities. *Journal of autism and developmental disorders*, *36*(5), 665-675.

Oblak, A. L., Gibbs, T. T., & Blatt, G. J. (2010). Decreased GABA-B receptors in the cingulate cortex and fusiform gyrus in Autism. *Journal of Neurochemistry*, *114*(5), 1414–1423.

Oblak, A. L., Gibbs, T. T., & Blatt, G. J. (2011). Reduced GABAA receptors and benzodiazepine binding sites in the posterior cingulate cortex and fusiform gyrus in autism. *Brain Res Cogn Brain Res*, *1380*, 218–228.

Oblak, A., Gibbs, T. T., & Blatt, G. J. (2009). Decreased GABAA receptors and benzodiazepine binding sites in the anterior cingulate cortex in autism. *Autism research : official journal of the International Society for Autism Research*, *2*(4), 205–19.

Orekhova, E. V., Stroganova, T. A., Nygren, G., Tsetlin, M. M., Posikera, I. N., Gillberg, C., & Elam, M. (2007). Excess of high frequency electroencephalogram oscillations in boys with

autism. *Biological psychiatry*,*62*(9), 1022-1029.

Orekhova, E. V., Stroganova, T. A., Prokofyev, A. O., Nygren, G., Gillberg, C., & Elam, M. (2008). Sensory gating in young children with autism: Relation to age, IQ, and EEG gamma oscillations. *Neuroscience Letters*, *434*(2), 218–223.

Page, L. A., Daly, E., Schmitz, N., Simmons, A., Toal, F., Deeley, Q., Ambery, F., et al. (2006). In vivo 1H-magnetic resonance spectroscopy study of amygdala-hippocampal and parietal regions in autism. *American Journal of Psychiatry*, *163*(12), 2189–2192.

Pizzarelli, R., & Cherubini, E. (2011). Alterations of GABAergic signaling in autism spectrum disorders. *Neural plasticity*, *2011*.

Purcell, a E., Jeon, O. H., Zimmerman, a W., Blue, M. E., & Pevsner, J. (2001). Postmortem brain abnormalities of the glutamate neurotransmitter system in autism. *Neurology*, *57*(9), 1618–1628.

Puts, N. A. J., & Edden, R. A. E. (2012). In vivo magnetic resonance spectroscopy of GABA: A methodological review. *Progress in Nuclear Magnetic Resonance Spectroscopy*, *60*, 29–41.

Robertson, C. E., Kravitz, D. J., Freyberg, J., Baron-Cohen, S., & Baker, C. I. (2013). Slower rate of binocular rivalry in autism. *The Journal of Neuroscience*, *33*(43), 16983–16991.

Robertson, C. E., Ratai, E.-M., & Kanwisher, N. (2015). Reduced GABAergic Action in the Autistic Brain. *Current Biology*, *26*(1), 80–85.

Rojas, D. C., Becker, K. M., & Wilson, L. B. (2014). Magnetic Resonance Spectroscopy Studies of Glutamate and GABA in Autism: Implications for Excitation-Inhibition Imbalance Theory. *Current Developmental Disorders Reports*, *2*, 46–57.

Rojas, D. C., Maharajh, K., Teale, P., & Rogers, S. J. (2008). Reduced neural synchronization of gamma-band MEG oscillations in first-degree relatives of children with autism. *BMC psychiatry*, *8*(1), 66.

Rojas, D. C., Singel, D., Steinmetz, S., Hepburn, S., & Brown, M. S. (2014). Decreased left perisylvian GABA concentration in children with autism and unaffected siblings. *Neuroimage*, *86*, 28-34.

Rolf, L. H., Haarmann, F. Y., Grotemeyer, K. H., & Kehrer, H. (1993). Serotonin and amino acid content in platelets of autistic children. *Acta psychiatrica Scandinavica*, *87*(4 C), 312–316.

Rossi, P. G., Parmeggiani, A., Bach, V., Santucci, M., & Visconti, P. (1995). EEG features and epilepsy in

patients with autism. *Brain and Development*, *17*(3), 169–174.

Rubenstein, J. L., & Merzenich, M. M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes, brain, and behavior*, *2*(5), 255—267.

Said, C. P., & Heeger, D. J. (2013). A Model of Binocular Rivalry and Cross-orientation Suppression. *PLoS Computational Biology*, *9*(3).

Said, C. P., Egan, R. D., Minshew, N. J., Behrmann, M., & Heeger, D. J. (2013). Normal binocular rivalry in autism: Implications for the excitation/inhibition imbalance hypothesis. *Vision Research*, *77*, 59–66.

Saxena, N., Muthukumaraswamy, S. D., Diukova, A., Singh, K., Hall, J., & Wise, R. (2013). Enhanced stimulus-induced gamma activity in humans during propofol-induced sedation. *PLoS One*, *8*(3), e57685.

Schwarzkopf, D. S., Anderson, E. J., de Haas, B., White, S. J., & Rees, G. (2014). Larger Extrastriate Population Receptive Fields in Autism Spectrum Disorders. *Journal of Neuroscience*, *34*(7), 2713–2724.

Seely, J., & Chow, C. C. (2011). Role of mutual inhibition in binocular rivalry. *Journal of Neurophysiology*, *106*(5), 2136–2150.

Shafai, F., Armstrong, K., Iarocci, G., & Oruc, I. (2015). Visual orientation processing in autism spectrum disorder: No sign of enhanced early cortical function. *Journal of Vision*, *15*(15), 18.

Shimmura, C., Suzuki, K., Iwata, Y., Tsuchiya, K. J., Ohno, K., Matsuzaki, H., Iwata, K., et al. (2013). Enzymes in the glutamate-glutamine cycle in the anterior cingulate cortex in postmortem brain of subjects with autism. *Molecular autism*, *4*(1), 6.

Sillito, A. M. (1975). The contribution of inhibitory mechanisms to the receptive field properties of neurones in the striate cortex of the cat. *The Journal of physiology*, *250*(2), 305–29.

Snijders, T. M., Milivojevic, B., & Kemner, C. (2013). Atypical excitation-inhibition balance in autism captured by the gamma response to contextual modulation. *NeuroImage: Clinical*, *3*, 65–72.

Sokhadze, E. M., El-Baz, A., Baruth, J., Mathai, G., Sears, L., & Casanova, M. F. (2009). Effects of low frequency repetitive transcranial magnetic stimulation (rTMS) on gamma frequency oscillations

and event-related potentials during processing of illusory figures in autism. *Journal of autism and developmental disorders*, *39*(4), 619-634.

Stanutz, S., Wapnick, J., & Burack, J. A. (2014). Pitch discrimination and melodic memory in children with autism spectrum disorders. *Autism*, *18*(2), 137–147.

Stroganova, T. A., Orekhova, E. V., Prokofyev, A. O., Tsetlin, M. M., Gratchev, V. V., Morozov, A. A., & Obukhov, Y. V. (2012). High-frequency oscillatory response to illusory contour in typically developing boys and boys with autism spectrum disorders. *Cortex*, *48*(6), 701–717.

Sun, L., Gru, C., Bo, S., Wibral, M., Tozman, T., Schlitt, S., Poustka, F., et al. (2012). Impaired Gamma-Band Activity during Perceptual Organization in Adults with Autism Spectrum Disorders: Evidence for Dysfunctional Network Activity in Frontal-Posterior Cortices. *The Journal of Neuroscience*, *32*(28), 9563–9573.

Tabuchi, K., Blundell, J., Etherton, M. R., Hammer, R. E., Liu, X., Powell, C. M., & Südhof, T. C. (2007). A neuroligin-3 mutation implicated in autism increases inhibitory synaptic transmission in mice. *Science*, *318*(5847), 71–6.

Tadin, D., Lappin, J. S., Gilroy, L. a, & Blake, R. (2003). Perceptual consequences of centre – surround antagonism in visual motion processing. *Nature*, *424*, 312–315.

Traub, R. D., Spruston, N., Soltesz, I., Konnerth, A., Whittington, M. A., & Jefferys, J. G. (1998). Gamma-frequency oscillations: a neuronal population phenomenon, regulated by synaptic and intrinsic cellular processes, and inducing synaptic plasticity. *Progress in neurobiology*, *55*(6), 563-575.

van Diessen, E., Senders, J., Jansen, F. E., Boersma, M., & Bruining, H. (2015). Increased power of resting-state gamma oscillations in autism spectrum disorder detected by routine electroencephalography. *European archives of psychiatry and clinical neuroscience*, *265*(6), 537-540.

van Elst, L. T., Maier, S., Fangmeier, T., Endres, D., Mueller, G. T., Nickel, K., ... & Riedel, A. (2014). Disturbed cingulate glutamate metabolism in adults with high-functioning autism spectrum disorder: evidence in support of the excitatory/inhibitory imbalance hypothesis. *Molecular psychiatry*, *19*(12), 1314-1325.

van Loon, A. M., Knapen, T., Scholte, H. S., John-Saaltink, E. S., Donner, T. H., & Lamme, V. A. (2013). GABA shapes the dynamics of bistable perception. *Current Biology*, *23*(9), 823-827.

van Pelt, S., Boomsma, D. I., & Fries, P. (2012). Magnetoencephalography in Twins Reveals a Strong Genetic Determination of the Peak Frequency of Visually Induced Gamma-Band Synchronization. *Journal of Neuroscience*, *32*(10), 3388–3392.

Wang, J., Caspary, D., & Salvi, R. J. (2000). GABA-A antagonist causes dramatic expansion of tuning in primary auditory cortex. *Neuroreport*, *11*(5), 1137–40.

Wang, J., Ding, D., & Salvi, R. J. (2002). Functional reorganization in chinchilla inferior colliculus associated with chronic and acute cochlear damage. *Hearing research*, *168*(1), 238-249.

Wheatstone, C. (1850). Contributions to the Physiology of Vision.Part II. On Some Remarkable, and Hitherto Unobserved, Phaenomena of Binocular Vision. *Proceedings of the Royal Society of London*, *6*, 138–141.

Whittington, M. A., & Traub, R. D. (2003). Interneuron diversity series: inhibitory interneurons and network oscillations in vitro. *Trends in neurosciences*, *26*(12), 676-682.

Whittington, M. A., Traub, R. D., Kopell, N., Ermentrout, B., & Buhl, E. H. (2000). Inhibition-based rhythms: experimental and mathematical observations on network dynamics. *International journal of psychophysiology*,*38*(3), 315-336.

Wilson, H. R., Blake, R., & Lee, S. H. (2001). Dynamics of travelling waves in visual perception. *Nature*, *412*(6850), 907–910.

Wilson, T. W., Rojas, D. C., Reite, M. L., Teale, P. D., & Rogers, S. J. (2007). Children and adolescents with autism exhibit reduced MEG steady-state gamma responses. *Biological psychiatry*, *62*(3), 192-197.

Wright, B., Alderson-Day, B., Prendergast, G., Bennett, S., Jordan, J., Whitton, C., Gouws, A., et al. (2012). Gamma activation in young people with autism spectrum disorders and typically-developing controls when viewing emotions on faces. *PLoS ONE*, *7*(7).

Yasuhara, A. (2010). Correlation between EEG abnormalities and symptoms of autism spectrum disorder (ASD). *Brain and Development*, *32*(10), 791–798.

Yip, J., Soghomonian, J. J., & Blatt, G. J. (2007). Decreased GAD67 mRNA levels in cerebellar Purkinje cells in autism: Pathophysiological implications. *Acta Neuropathologica*, *113*(5), 559–568.

Yizhar, O., Fenno, L. E., Prigge, M., Schneider, F., Davidson, T. J., O'Shea, D. J., Sohal, V. S., et al. (2011). Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature*, *477*(7363), 171–178.