The contribution of [1H] magnetic resonance spectroscopy to the study of excitation-inhibition in autism

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\textbf{ABSTRACT}

Autism spectrum disorder (ASD) affects over 1:100 of the population and costs the UK more than £32bn and the USA more than $175bn (€104bn) annually. Its core symptoms are social and communication difficulties, repetitive behaviours and sensory hyper- or hypo-sensitivities. A highly diverse phenotypic presentation likely reflects its etiological heterogeneity and makes finding treatment targets for ASD challenging. In addition, there are no means to identify biologically responsive individuals who may benefit from specific interventions. There is hope however, and in this review we consolidate how findings from magnetic resonance spectroscopy (MRS) add to the evidence that differences in the brain’s excitatory glutamate and inhibitory γ-aminobutyric acid (GABA) balance may be both a key biomarker and a tractable treatment target in ASD.

\section{1. Introduction}

Autism spectrum disorder (ASD) is a highly heterogeneous lifelong neurodevelopmental syndrome characterised by deficits in social reciprocity and communication, and by restricted interests and stereotyped behaviours (DSM-5; \textit{American Psychiatric Association}, 2013). Its prevalence is growing (\textit{Lai et al.}, 2014) and, in the UK alone, adults with ASD cost the economy over £32 billion/year, i.e. more than heart disease, cancer and stroke combined (\textit{Buescher et al.}, 2014). Therefore, there is a pressing need to identify the underlying biological mechanisms that would provide a basis for the development of ASD stratification markers and treatment options. Progress is happening however, based on accumulating evidence that multiple genetic and environmental risk factors for ASD converge to disrupt the balance between glutamate-mediated excitatory and γ-aminobutyric acid (GABA)-mediated inhibitory neurotransmission; and this may inform treatment targets for the disorder (\textit{Nelson and Valakh}, 2015; \textit{Rubenstein and Merzenich}, 2003).

\section{2. Evidence for excitation-inhibition imbalance in autism spectrum disorder}

A balanced interaction between glutamate and GABA is essential for synaptic maturation, refinement of neuronal circuitry and subsequently the regulation of cognition, emotion and behaviour (\textit{Lujan et al.}, 2005). An imbalance in excitation-inhibition (E-I) caused by disruption to any component of the glutamate and GABA signalling systems could therefore have potentially far-reaching consequences. Indeed, based on observations such as an increased incidence of epilepsy – a disorder of E-I balance – in individuals with ASD (\textit{Bolton et al.}, 2011; \textit{Muhle et al.}, 2004), and post-mortem evidence of altered expression of proteins involved in glutamate and GABA biosynthesis and neurotransmission in the brains of individuals with ASD (\textit{Blatt and Fatemi}, 2011; \textit{Fatemi et al.}, 2002, 2009, 2014; \textit{Oblak et al.}, 2009, 2010, 2011; \textit{Purcell et al.}, 2001; \textit{Shimmura et al.}, 2013; \textit{Yip et al.}, 2007), E-I imbalance has been suggested to be a ‘common final pathway’ in ASD (\textit{Nelson and Valakh}, 2015; \textit{Rubenstein and Merzenich}, 2003).
Genetic studies are in line with this proposal. For example, studies of ASD susceptibility genes have repeatedly identified chromosome 15q11-13 as a particular region of interest as 1–3% of all ASD cases were reported to be associated with duplications in this region (Moreno-De-Luca et al., 2013; Urraca et al., 2013). This chromosomal region contains genes for three GABA<sub>A</sub> receptor subtype genes (i.e. β3, γ3 and α5). Mutations in this region, especially in the β3 subunit, convey a high risk for ASD and have been linked to repetitive symptoms and insistence on sameness (Chaste et al., 2014; Isles et al., 2016; Shao et al., 2003). Direct evidence for the link between GABA<sub>A</sub>-β3 and ASD has also been generated from a β3 knock-out mouse. These mice have behaviours analogous to the condition; they also have seizures, which are a frequent comorbid complication of ASD caused by E-I imbalance (DeLorey et al., 1991). FMRP negatively regulates postsynaptic glutamate receptor synthesis (including metabotropic glutamate receptor 5; mGlur5) by binding to ribosomes and stalling translation of target mRNAs (Darnell et al., 2011). mRNA translation at the synapse is then increased (Bear et al., 2004), leading to excess excitatory activity, enhanced long term depression, and ASD-like pathology in animal models (Lozano et al., 2013; Uchino and Waga, 2015; Xing et al., 2016). Lower levels of FMRP cause) who have a concomitant increase in mGluR5 (Fatemi et al., 2002; Shimura et al., 2013; Yip et al., 2007), and so glutamine-glutamate-GABA metabolism is likely to be atypical in the ASD brain.

How these diverse E-I anomalies might act mechanistically has been the subject of a number of recent comprehensive reviews (Foss-Feig et al., 2017; Gao and Penes, 2015; Gatto and Brodiale, 2010; Lee et al., 2017; Mullins et al., 2016; Nelson and Valakh, 2015; Uzunova et al., 2016). For example, Yizhar et al. (2011) have shown that increase of a cellular E-I balance in the mouse medial prefrontal cortex (mPFC) elicits elevated rhythmic high-frequency (gamma) activity (a disease correlate in clinical conditions; Orekhova et al., 2007) and social dysfunction. Furthermore, it was recently shown that reducing the E-I ratio by either reducing the excitability of pyramidal neurons or by increasing the excitability of inhibitory parvalbumin-positive neurons in the mPFC rescued social deficits in mice lacking the CNTNAP2 gene, which has been implicated in ASD (Selimideyoglu et al., 2017). Maintenance of E-I balance is thus essential to network function as not only functional, but also structural properties of neural circuits are defined by inter-neuronal communication.

### 3. [1H] Magnetic resonance spectroscopy evidence for E-I imbalance in ASD

The hypothesis that the glutamine-glutamate-GABA system is altered in ASD has also been addressed by using [1H] magnetic resonance spectroscopy (MRS) as a non-invasive method to measure tissue levels of E-I metabolites in the living human brain (Ford and Crewther, 2016; Schur et al., 2016). In brief, [1H]MRS uses the nuclear magnetic resonance properties of hydrogen atoms to generate a frequency spectrum (as opposed to the image in MR imaging) (Govindaraju et al., 2000; Juchem and Rothman, 2014; Stagg et al., 2011) in which different metabolites are identified by the position of their signal peak, i.e. chemical shift, along the frequency axis (in units of ‘parts per million’; ppm). [1H]MRS metabolite levels can then be quantified by calculating the area under the corresponding peaks or by fitting the in vivo spectra to a basis set, i.e. linear combinations of measured or simulated model spectra of metabolites (Edden et al., 2014; Naressi et al., 2001; Provencher, 1993). [1H]MRS is not without limitations however. For an adequate signal-to-noise ratio, standard single voxel [1H]MRS data is acquired from a predefined and relatively large brain volume-unit (usually around 4–8 mm<sup>3</sup>) (Stagg et al., 2011; Zhu and Barker, 2011) compared with conventional MR image resolution (typically around 1–10 mm<sup>3</sup>) (Blüml, 2013). Therefore, both grey and white matter is usually sampled within the same voxel. To avoid errors when quantifying metabolites, these so-called ‘partial volume’ effects need to be corrected by segmenting spectroscopic voxel according to different tissue contents (Dager et al., 2008; Quadrelli et al., 2016). As shown in Table 1, most of the studies reported using tissue segmentation, however, exact approaches varied considerably between studies which might contribute to inconsistencies in the literature. Such partial volume effects are minimised in [1H]MRS imaging (MRSI), a less frequently used extension of [1H]MRS that allows data from multiple adjacent small (1 cm<sup>3</sup> and below) voxels to be acquired simultaneously (Blüml, 2013; Ox et al., 2014; Schneider, 2016; Zhu and Barker, 2011).
| Citation               | ASD group N | Age (years) | [1H] MRSI sequence (TR/TE/TAv) | Quantiﬁcation method (tissue segmentation) | Brain areas investigated (cm³) | Metabolite concentrations in ASD participants compared with controls |
|-----------------------|-------------|-------------|-------------------------------|---------------------------------------------|-----------------------------|---------------------------------------------------------------------|
|                        |             |             |                               |                                             |                             | G	extsubscript{lx} | Glu | GABA+ |
| Pediatric studies     |             |             |                               |                                             |                             |                        |      |       |
| Friedman et al. (2006) | 45          | 3–4         | 1.5 T MRSI PEPSI (2000/20,27/na) | Estimated concentration (Y)                | Grey matter (na)            | NSD na na |
| DeVito et al. (2007)  | 26          | 6–17        | 3 T MRSI (1800/135/na)         | Estimated concentration (Y)                | Grey matter (na)            | NSD na na |
| Hardan et al. (2008)  | 18          | 8–15        | 1.5 T MRSI STEAM (1600/20/4)   | Estimated concentration (Y)                | Grey matter (na)            | NSD na na |
| Harada et al. (2011)  | 12          | 2–11        | 3 T STEAM (3000/15/48)         | Estimated concentration (Y)                | Grey matter (na)            | NSD na na |
| Bejjani et al. (2012) | 8           | 7–15        | 1.5 T PRESS (1500/25/256)      | Estimated concentration (Y)                | Grey matter (na)            | NSD na na |
| Kubs et al. (2012)    | 12          | 8–15        | 1.5 T PRESS (1500/35/192)      | Estimated concentration (na)               | Grey matter (na)            | NSD na na |
| Corrigan et al. (2013)| 31          | 6–7         | PEPSI (2000/20/na)             | Estimated concentration (na)               | Grey matter (na)            | NSD na na |
| Hassan et al. (2013)  | 10          | 6–14        | 1.5 T PRESS (1500/30/3)        | Estimated concentration (na)               | Grey matter (na)            | NSD na na |
| Doyle-Thomas et al. (2014) | 7     | 12–17       | 4 T 2D-JPRESS (2000/30-250/16,32) | Estimated concentration (Y)                | Grey matter (na)            | NSD na na |
| Gaez et al. (2014)    | 17          | 11          | 3 T MEGA-PRESS (1500/68/256)   | Estimated concentration (na)               | Grey matter (na)            | NSD na na |
| Rojas et al. (2014)   | 17          | 14          | 3 T MEGA-PRESS (2500/70/512)   | Estimated concentration (na)               | Grey matter (na)            | NSD na na |
| Brix et al. (2015)    | 14          | 10          | 3 T PRESS (1500/35/128)        | Estimated concentration (Y)                | Grey matter (na)            | NSD na na |
| Cochran et al. (2015) | 13          | 13–17       | 3 T PRESS (2000/28/128)        | Estimated concentration (Y)                | Grey matter (na)            | NSD na na |
| Drenthen et al. (2016)| 15          | 14–18       | 3 T PRESS (2000/35/128)        | Estimated concentration (Y)                | Grey matter (na)            | NSD na na |
| Nasjien et al. (2016) | 51          | 8–13        | 3 T PRESS (3000/30/96)         | Estimated concentration (Y)                | Grey matter (na)            | NSD na na |
| Goji et al. (2017)    | 34          | 2–12        | 3 T STEAM (5000/15/48)         | Estimated concentration (na)               | Grey matter (na)            | NSD na na |
| Hegarty et al. (2017) | 23          | 4–9         | 3 T PRESS (2500/68/256)        | Estimated concentration (Y)                | Grey matter (na)            | NSD na na |
|                       |             |             |                               |                                             |                             |                        |      |       |
| (continued on next page) |             |             |                               |                                             |                             |                        |      |       |
| Citation                        | ASD group | N  | Age (years) | [1H] MRS sequence (TR/TE/Av) | Quantification method (issue segmentation) | Brain areas investigated (cm³) | Metabolite concentrations in ASD participants compared with controls |
|--------------------------------|-----------|----|-------------|-----------------------------|---------------------------------------------|------------------------------|--------------------------------------------------|
| Ito et al. (2017)              | 112       | 4-14-6-14 | 3 T STEAM (3000/15/48) | Cerebral cortex (na) | Higher in ASD | Lower in ASD |
| Port et al. (2017)             | 16        | 6-14 | 3 T MEGA-PRESS (2500/68/256) | Cerebral cortex (na) | Higher in ASD | Lower in ASD |
| Port et al. (2017)             | 27        | 9-18 | 3 T MEGA-PRESS (2500/68/256) | Cerebral cortex (na) | Higher in ASD | Lower in ASD |
| Puts et al. (2017)             | 16        | 8-12 | 3 T MEGA-PRESS (2500/68/256) | Cerebral cortex (na) | Higher in ASD | Lower in ASD |
| Cavalho Pereira et al. (2018)  | 176       | 9-18 | 3 T MEGA-PRESS (2500/68/256) | Cerebral cortex (na) | Higher in ASD | Lower in ASD |
| Page et al. (2006)             | 8         | 3 T PRESS (3000/35/160) | Estimated concentration (Y) | Auditory cortex (24) | Higher in ASD | Lower in ASD |
| Bernard et al. (2013)          | 13        | 3 T PRESS (3000/30/na) | Estimated concentration (Y) | Auditory cortex (24) | Higher in ASD | Lower in ASD |

Notes: Metabolite concentrations refer to water- or external reference-scaled metabolites. ASD: autism spectrum disorder; Av: number of averages; GABA+; γ-aminobutyric acid + macromolecules; Glx: glutamate + glutamine; Glu: glutamate; L: left; MRS: magnetic resonance spectroscopy imaging; MEGA-PRESS: Multiecho gradient-echo point-resolved spectroscopy imaging; PRESS: point-resolved spectroscopy; R: right; ROI: region of interest; STEAM: stimulated echo acquisition mode; TR: repetition time (ms); TE: echo time (ms).
However, MRSI is often associated with reduced spectral resolution, non-uniform water suppression and voxel bleeding artefact (i.e. signal contamination from neighbouring voxels into the voxel-of-interest), therefore single voxel [1H]MRS remains the technique of choice (Astrakas and Argyropoulou, 2016; Bliuml, 2013; Duarte et al., 2012; Jansen et al., 2006).

This large volume also means that [1H]MRS samples tissue metabolites within both neurons and glia and in both intra- and extra-cellular space (Dager et al., 2008). Therefore, to account for possible variation in voxel tissue composition, some studies report metabolite concentrations as ratios to total creatine (creatine + phosphocreatine; tCr), which is assumed to be present at constant concentration in brain tissue and cerebrospinal fluid (Gussew et al., 2012). However, as an alternative to tCr ratios, water has been used as a reference because tCr itself can be altered in neurodevelopmental conditions (Alger, 2010). Finally, depending on technical factors, such as the magnetic field strength, it is not always possible to differentiate between glutamate and glutamine due to the overlap of their resonant peaks, and the combined signal termed Glx is commonly reported (Table 1), and thus is only a proxy measure of glutamate. Similarly, the GABA signal usually also has a contribution from ‘macromolecules’, and is denoted as GABA+ (Edden et al., 2012; Henry et al., 2001; Mikkelsen et al., 2017; Near et al., 2011).

Despite these limitations, [1H]MRS is safe and therefore, in contrast to other in vivo imaging modalities such as positron emission tomography, it can be used repeatedly, and also in children. Indeed, many [1H]MRS studies of E-I metabolites in ASD have been conducted in paediatric populations. The initial studies focused on the glutamatergic system, reporting Glx and glutamate (Glu), with reduced levels found in the cortical grey matter, frontal lobes, thalamus and cerebellum in children with ASD (DeVito et al., 2007; Hegarty et al., 2017; Kubas et al., 2012) (Table 1). However, this was not replicated by others, with either no difference in Glx/Glu observed between ASD and control participants in cortical and subcortical areas (Brix et al., 2015; Cavalho Pereira et al., 2018; Cochran et al., 2015; Doyle-Thomas et al., 2014; Drenthen et al., 2016; Friedman et al., 2006; Goji et al., 2017; Harada et al., 2011; Hardan et al., 2008; Ito et al., 2017; Joshi et al., 2013; Naaijen et al., 2016) or higher levels reported in ASD – in the anterior cingulate cortex, frontal lobes, striatum (Bejani et al., 2012; Doyle-Thomas et al., 2014; Joshi et al., 2013; Hassan et al., 2013; Naaijen et al., 2016) and cerebellum (Hassan et al., 2013; Ito et al., 2017) (Table 1).

By definition, ASD is a neurodevelopmental condition and how the brain matures is acknowledged to be quite different to even age matched controls (Amaral et al., 2008; Aoki et al., 2012; Redcay and Courchesne, 2005). Thus, results of [1H]MRS studies in ASD – as other MR modalities – may vary depending on the age group sampled. For example, Corgian et al. (2013) have reported lower Glx in the cerebral white matter of 3–4-year-old children; however, there was no change in Glx when the same children were scanned again at age 6–7 and 9–10 years; and no difference in grey matter Glx at any age in childhood (Table 1). However, even in adulthood, when the brain may be expected to have fully matured, [1H]MRS studies of glutamate have generated conflicting findings. Lower Glx/Glu has been reported in the anterior cingulate cortex in ASD adults (Bernardi et al., 2011; Tebartz van Elst et al., 2014) (Table 1), but others have observed no significant difference in Glx between ASD adults and controls in this cortical region (Endres et al., 2017; Libero et al., 2015, 2016) (Table 1). Horder et al. (2013, 2018) reported lower Glx/Glu in the basal ganglia of adults with ASD, but unchanged cortical levels (Table 1).

In addition to differences in study samples and brain regions examined, different [1H]MRS sequences for quantification of Glx and/or Glu have been employed in the studies reviewed here (Table 1). While conventional [1H]MRS sequences (e.g. STEAM, PRESS) were used by most, unedited (equivalent to a PRESS) (Horder et al., 2018; Robertson et al., 2015) as well as the difference MEGA-PRESS spectra (edit OFF subtraction; please see below) (Ajram et al., 2017; Cavalho Pereira et al., 2018) were also used to quantify Glx and/or Glu (Table 1).

In order to sample GABA, customised spectral editing sequences, such as Mesecher-Garwood Point-resolved spectroscopy (MEGA-PRESS) carried out at 3 T or higher field strengths are required (Mesecher et al., 1998; Mullins et al., 2014). In MEGA-PRESS, a GABA signal can be resolved from the more prominent Cr + PCr signal at 3 ppm by applying an editing pulse (edit ON) to the GABA signal at 1.9 ppm interleaved with edit OFF pulse (no frequency-selective editing pulses applied, or if applied, at a different frequency) (Cleve et al., 2015; Long et al., 2015; Maddock et al., 2016; Mescher et al., 1998; Mullins et al., 2014; Shungu et al., 2016). The application of this editing pulse results in the co-editing of other molecules present in the final spectrum, namely the Glx at 3.75 ppm and ‘macromolecules’ at 3 ppm (Cleve et al., 2015; O’Gorman et al., 2011). Thus, the GABA signal at 3 ppm is commonly reported as GABA+ (Table 1). Furthermore, due to low tissue concentration of GABA, MEGA-PRESS requires larger ROI volumes (typically around 27 cm3) and longer acquisition times ideally between 7 and 10 min (Mikkelsen et al., 2018). This was generally applied in all but two reviewed study (Kirovski et al., 2018; Kubas et al., 2012) (Table 1). In ASD, most studies of [1H]MRS GABA+ have been conducted only in the last four years (Table 1). The majority have recruited children (Brix et al., 2015; Cavalho Pereira et al., 2018; Cochran et al., 2015; Drenthen et al., 2016; Gaetz et al., 2014; Goji et al., 2017; Harada et al., 2011; Ito et al., 2017; Kubas et al., 2012; Puts et al., 2017; Rojas et al., 2014), with three studies involving only adults (Ajram et al., 2017; Horder et al., 2018; Kirovski et al., 2018; Robertson et al., 2015), and one combining children and adults (Port et al., 2017). The pattern of GABA+ differences in ASD compared to typically developing controls is a little more consistent than for Glx and Glu, with either lower or no difference in regional GABA+ reported. Thus, lower GABA+ has been found in the motor, auditory and frontal cortices and in the sensorimotor regions, anterior cingulate cortex and cerebellum (Gaetz et al., 2014; Harada et al., 2011; Ito et al., 2017; Kubas et al., 2012; Port et al., 2017; Puts et al., 2017; Rojas et al., 2014), whereas others have observed no differences in GABA+ in the prefrontal and occipital cortices (Ajram et al., 2017; Brix et al., 2015; Cavalho Pereira et al., 2018; Cochran et al., 2015; Drenthen et al., 2016; Gaetz et al., 2014; Goji et al., 2017; Horder et al., 2018; Puts et al., 2017; Robertson et al., 2015), lenticular nuclei (Harada et al., 2011), motor cortex (Robertson et al., 2015), superior temporal sulcus (Kirovski et al., 2018), basal ganglia (Horder et al., 2018) and cerebellum (Goji et al., 2017) (Table 1).

Reduction in GABA in the somatosensory cortex has been associated with altered tactile function in children with ASD (Puts et al., 2017). Interestingly, developmental tactile perception abnormalities due to a loss of presynaptic inhibition of somatosensory neuron transmission have been shown to result in ASD-related social interaction deficits in mice (Orefice et al., 2016). However, even in the absence of group differences in GABA+, a role for GABA in ASD has still been argued based on findings that [1H]MRS GABA+ levels in ASD are inversely correlated with scores on the Autism Spectrum Screening Questionnaire (Brix et al., 2015) and with the communication and delayed development scores of the Autism Diagnostic Interview – Revised (Cavalho Pereira et al., 2018). More difficult to disentangle are the results from Robertson et al. (2015). In their study, occipital GABA+ measures were equivalent in ASD and control groups, but the ASD group had a deficit in the performance of a binocular rivalry task of visual function thought to rely upon visual cortical E-I balance. The authors went on to show that a positive correlation between GABA+ and performance on a binocular rivalry task in control group was not evident in the ASD group, and suggested that the results supported an impairment in ‘inhibitory signalling’ in ASD (Robertson et al., 2015). This may well be the case, but because [1H]MRS captures the metabolites within a composite of cell types and does not capture active neurotransmission, it is
impossible to say with certainty.

4. E-I flux in ASD

One perspective on this constellation of [1H]MRS findings in ASD, is that their range may mirror the etiological and phenotypical heterogeneity of the spectrum as well as the variety in the typically developing control groups used for comparison. For example, [1H]MRS measures of glutamate and GABA+ differ even within the typically developing population (Bogner et al., 2010; Brix et al., 2017; Kaiser et al., 2005; O’Gorman et al., 2011; Sillasuta et al., 2008).

Another consideration for the field is that, in the main, indices of glutamate and GABA have been assessed separately in ASD; yet the results have been interpreted in terms of E-I balance (Dickinson et al., 2016). It could be argued that a true imbalance can only be uncovered if the level of each metabolite is reported. Thus, if a GABA decrease is accompanied by a glutamate decrease, then the system may remain balanced. Moreover, until recently, the logic of trying to capture metabolites within a glutamine-glutamate-GABA cycle that is constantly changing or in ‘flux’ in cohorts with and without ASD, has not been questioned. We now suggest that replication difficulties in cross-sectional studies of glutamate and GABA pathways in ASD arise, at least in part, because they sample only one part of an E-I system, which is a ‘moving target’. As described earlier, the regulatory enzymes controlling this dynamic system are altered in ASD, and so E-I flux in ASD is therefore very likely to be atypical.

Supporting this hypothesis, there is now evidence that [1H]MRS is sensitive to changes in E-I flux elicited by pharmacological probes that challenge the system. This comes initially from studies in rats, which have established that [1H]MRS can reliably capture changes in glutamate and GABA levels following pharmacological interventions (Waschkies et al., 2014). Specifically, [1H]MRS was used to track the E-I response to pharmacologically relevant doses of compounds with a known mechanism of action on GABAergic and glutamatergic neurotransmission, namely vigabatrin, 3-mercaptopropionate, tiagabine, methionine sulfoximine, and riluzole. Clear drug dose–[1H]MRS effect relationships were demonstrated, with changes as low as 6% in glutamate and 12% in GABA reliably measured using [1H]MRS. The authors concluded that quantitative [1H]MRS of glutamate and GABA may usefully reveal E-I ‘target engagement’ – in other words, the interaction of a drug with its biological goal (Waschkies et al., 2014). We have recently extended this approach to humans. Using [1H]MRS, we found that the anti-glutamate and pro-GABA drug riluzole increased the flux elicited by pharmacological probes that sensitively to changes in E-I

5. Conclusions

We conclude that disruption within E-I systems could serve as a biomarker for ASD. However, we extend this observation to suggest that E-I systems in the ASD brain are pharmacologically atypical. However, the picture is far from straight-forward. This means that we need better strategies, potentially including [1H]MRS, to examine the biological response or target engagement to proposed treatments in sub-groups of individuals with ASD. The identification of more pharmacologically homogeneous sub-groups within the spectrum may inform a new generation of biologically-driven clinical trials and avoid the time and expense (and failure) of un-stratified large-scale studies.

Author contributions

L.A.A., M.M.P., and G.M.M. designed the study. L.A.A., A.M.S.D., A.C.P., H.E.V., M.M.P., and G.M.M. wrote the manuscript. All authors contributed to and approved the final manuscript.

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Declarations of interest

None.

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Maturational and functional development of glutamatergic and GABAergic neuronal networks is critically important for the normal development of the central nervous system. Alterations in these networks can lead to a variety of neurological and psychiatric disorders. For example, autism spectrum disorder (ASD) is characterized by deficits in social interaction and communication, as well as restricted and repetitive behaviors. The pathophysiology of ASD is thought to involve abnormalities in synaptic transmission, neurotransmitter systems, and neural circuits.

In this context, several studies have investigated the role of glutamate and GABA in ASD. For instance, Lentz et al. (2005) found decreased levels of glutamate and GABA in the cerebrospinal fluid of children with ASD compared to controls. Similarly, Cuthbert et al. (2010) reported reduced GABA levels in the anterior cingulate cortex of ASD patients. These findings suggest that alterations in glutamatergic and GABAergic systems may contribute to the symptomatology of ASD.

Moreover, the role of these neurotransmitters in the development of ASD is further supported by the findings of several genetic studies. For example, the CNTNAP2 gene, which is associated with ASD, has been linked to abnormalities in glutamatergic transmission (Ozon et al., 2014). Additionally, mutations in the neurexin and neolinigin genes, which are involved in synaptic function, have been identified in ASD patients (Oblak et al., 2014).

In conclusion, understanding the role of glutamate and GABA in the development of ASD is crucial for identifying potential targets for intervention and developing effective treatment strategies. Further research is needed to elucidate the precise mechanisms underlying these alterations and to develop novel therapeutic approaches.
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