NeuroImage: Clinical 16 (2017) 125–131

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Increased glutamate/GABA+ ratio in a shared autistic and schizotypal trait phenotype termed Social Disorganisation

Talitha C. Ford[a,*], Richard Nibbs[b], David P. Crewther[a]

[a] Centre for Human Psychopharmacology, Faculty of Heath, Arts and Design, Swinburne University of Technology, Melbourne, Victoria, Australia
[b] Swinburne Neuroimaging, Faculty of Heath, Arts and Design, Swinburne University of Technology, Melbourne, Victoria, Australia

ARTICLE INFO

Keywords:
^{1}H-MRS
Glutmate
GABA
Autism
Schizophrenia
Social Disorganisation

ABSTRACT

Autism and schizophrenia are multi-dimensional spectrum disorders that have substantial phenotypic overlap. This overlap is readily identified in the non-clinical population, and has been conceptualised as Social Disorganisation (SD). This study investigates the balance of excitatory glutamate and inhibitory γ-aminobutyric acid (GABA) concentrations in a non-clinical sample with high and low trait SD, as glutamate and GABA abnormalities are reported across the autism and schizophrenia spectrum disorders.

Participants were 18 low (10 females) and 19 high (9 females) SD scorers aged 18 to 40 years who underwent ^{1}H-MRS for glutamate and GABA+macromolecule (GABA+) concentrations in right and left hemisphere superior temporal (ST) voxels.

Reduced GABA+ concentration ($p = 0.03$) and increased glutamate/GABA+ ratio ($p = 0.003$) in the right ST voxel for the high SD group was found, and there was increased GABA+ concentration in the left compared to right ST voxel ($p = 0.047$). Bilateral glutamate concentration was increased for the high SD group ($p = 0.006$); there was no hemisphere by group interaction ($p = 0.772$).

Results suggest that a higher expression of the SD phenotype may be associated with increased glutamate/GABA+ ratio in the right ST region, which may affect speech prosody processing, and lead behavioural characteristics that are shared within the autistic and schizotypal spectra.

1. Introduction

Autism and schizophrenia spectrum disorders are reported to share interpersonal and communication difficulties at a clinical and non-clinical level (Dinsdale et al., 2013; Spek and Wouters, 2010). Much of this overlap has been identified through the use of self-report scales, such as the autism spectrum quotient (AQ; Baron-Cohen et al., 2001) and schizotypal personality questionnaire (SPQ; Raine, 1991), that measure the core dimensions of the respective disorders. Within the non-clinical population, factor analysis of the AQ and SPQ subscales has demonstrated a shared trait phenotype, with the first factor comprising negative and disorganised symptom traits of the SPQ, and social and interpersonal difficulty traits of the AQ; this trait phenotype was coined Social Disorganisation (Ford and Crewther, 2014).

Previous studies suggest potential cortical underpinnings of this shared phenotype at a clinical level (Pinkham et al., 2008; Sugranyes et al., 2011), and abnormal levels of neurochemicals such as glutamate and γ-aminobutyric acid (GABA), which are involved in cortical excitatory/inhibitory processes, have been reported in both autism and schizophrenia spectrum disorders (Robertson et al., 2016; Rojas et al., 2014; Brown et al., 2013; Marsman et al., 2014; Tebartz van Elst et al., 2014; Horder et al., 2013; Harada et al., 2011). Furthermore, psychosocial dysfunction – the central feature of the Social Disorganisation phenotype – has been associated with an increased excitation/inhibition ratio (Yizhar et al., 2011). Finally, auditory processing deficits are reported across the autism and schizophrenia spectra (Kompus et al., 2015; Gandal et al., 2012; Rossignol, 2011; Ford et al., 2017a; Ford et al., 2017b), and these deficits have been related to glutamate and GABA concentrations (Kompus et al., 2015), and social and interpersonal impairment (Fulham et al., 2014; Rasser et al., 2011).

Glutamate is the primary excitatory neurotransmitter (McKenna et al., 2011) and plays a crucial role in neural functioning (Danbolt, 2001). Glutamate is synthesised from glutamine via the enzyme glutaminase in glutamatergic neurons, as well as in astrocytes (Bak et al., 2006; McKenna, 2007). Although mostly intracellular, glutamate constantly cycles between extracellular and intracellular space (Danbolt, 2001). Inhibitory GABA, synthesised from glutamate via the enzyme glutamic acid decarboxylase (GAD), regulates glutamatergic excitation.

* Corresponding author.
E-mail addresses: tcford@swin.edu.au (T.C. Ford), rnibbs@swin.du.au (R. Nibbs), dcrewther@swin.edu.au (D.P. Crewther).

http://dx.doi.org/10.1016/j.nicl.2017.07.009
Received 12 April 2017; Received in revised form 19 June 2017; Accepted 12 July 2017
Available online 24 July 2017

Together, glutamate/GABA regulation is essential for neural migration, differentiation and plasticity (Stagg et al., 2011; Rossignol, 2011; Danbolt, 2001).

Cortical glutamate and GABA are low molecular weighted metabolites that can be quantified using proton magnetic resonance spectroscopy (^{1}H-MRS), which separates metabolites along a chemical shift spectrum (Ford and Crewther, 2016; Juchem and Rothman, 2014). However, glutamate, glutamine and GABA are often reported as a single Glx concentration due to their co-dependence and subsequently overlapping spectral peaks (Juchem and Rothman, 2014; Stagg et al., 2011, 2009). The isolation and quantification of overlapping metabolites is dependent upon scanner strength and pulse sequence methods (Ford and Crewther, 2016; Stagg et al., 2009; Schubert et al., 2004). A long echo time (TE) point resolved spectroscopy (PRESS) ^{1}H-MRS sequence at 3T has been shown to successfully distinguish glutamate from glutamine, GABA and N-acetylaspartate spectral peaks (Schubert et al., 2004). Similarly, to isolate GABA, the Meshcher-Garwood (MEGA)-PRESS editing sequence is reliably used (Mescher et al., 1998). ^{1}H-MRS, however, is only capable of quantifying the tissue concentration of metabolites (Marsman et al., 2013; Stagg et al., 2011, 2009), not functional cortical excitation and inhibition.

Among clinical samples, a higher concentration of Glx in the temporal lobe has been related to greater severity of autistic symptoms and negative symptoms of schizophrenia (Brown et al., 2013; Szulc et al., 2005), and higher glutamate concentration in the auditory cortex has been reported in autism studies (Brown et al., 2013). Increased anterior cingulate glutamate/creatine and Glx have been related to more negative symptoms, and social and communication deficits (Egerton et al., 2012; Tebartz van Elst et al., 2014), while the contrary was found in the parieto-occipital region and basal ganglia (Horder et al., 2013; Marsman et al., 2014). The hyper-glutamatergic hypothesis of autism presented by Fatemi (2008) suggests that a deficit in the GABA synthesising enzyme, GAD, and the presence of more astrocytes that take up synaptic glutamate to resynthesise glutamine and glutamate, leads to excess glutamate in autistic cortices (Fatemi et al., 2002).

In addition to hyper-glutamatergia, Fatemi et al. (2009) suggest a theory of $GABA_A$ receptor down-regulation for autism, whereby mediation of GABA inhibition is reduced leading to cortical disinhibition. $GABA_A$ receptor dysfunction has also been implicated in an cortical excitation/inhibition imbalance in schizophrenia (Fatemi et al., 2009), and reduced GABA concentration and GABA/creatine has been reported in autism (Coghlan et al., 2012; Rojas et al., 2014; Harada et al., 2011) and schizophrenia (Marsman et al., 2014).

An imbalance in the excitation/inhibition ratio has also been widely attributed to *N*-methyl-D-aspartate receptor (NMDAr) hypo-function, particularly across the schizophrenia spectrum. NMDArs receive glutamate to activate glutamatergic and GABAergic neurons (Marsman et al., 2014; Lisman et al., 2008). Hypo-function of these receptors reduces the inhibitory output of GABAergic interneurons, and increases cortical excitation through disinhibition of excitatory neurons (Lisman et al., 2008). Furthermore, NMDArs have been implicated in auditory processing deficits that are seen across both spectrum disorders (Kantrowitz and Javitt, 2010).

In sum, clinical and non-clinical traits symptoms of autism and schizophrenia have consistently been shown to overlap, and symptoms have been associated with auditory processing and neurochemical differences. This study, therefore, explores glutamate and GABA concentration differences in bilateral superior temporal regions, including the auditory cortex, between non-clinical individuals reporting a high compared to a low degree of the Social Disorganisation phenotype. It was predicted that glutamate concentration would be significantly higher and GABA concentration would be significantly lower for those reporting high Social Disorganisation compared to those reporting low Social Disorganisation. It was also hypothesised that the ratio of glutamate to GABA would be higher for the high Social Disorganisation group.

Table 1
Participant demographic information (mean (SD)).

	Low		High	
	Male	Female	Male	Female
n	8	10	10	9
Age (years)	25.75 (7.13)	22.9 (7.13)	22.2 (4.61)	22 (4.61)
Social Dis. (*z*-score)	−1.3 (0.27)	−1.45 (0.27)	1.5 (0.54)	1.42 (0.54)
AQ (/200)	94.12 (8.15)	92.6 (8.15)	130.2 (10.16)	132.56 (10.16)
SPQ (/296)	109.88 (11.91)	107.8 (11.91)	187.1 (16.53)	188 (16.53)

Social Dis. = Social Disorganisation.

2. Method

2.1. Participants

Ethics approval was granted by the Swinburne University Human Research Ethics Committee (2011/033 Series C(d)). All participants provided written informed consent before commencing the study. A total of 1678 participants (428 males, 1250 females, age 18–40) completed the autism schizotypy questionnaire (ASQ). From the large pool of participants, 37 participated in the ^{1}H-MRS study. Demographic information is presented in Table 1. No participants in the low Social Disorganisation group reported a personal psychiatric history. In the high group, five participants reported a psychiatric history (3 depression, 1 bipolar, 1 anorexia); there were no self-reports of a history of autism or schizophrenia, and all claimed to be unaffected at the time of the scan. Participants were excluded if they were currently taking psychoactive medications.

There were no sex or group differences in intelligence as measured by the Raven's advanced progressive matrices short form (Arthur and Day, 1994). Smoking behaviour was recorded (high: male = 1 × 1/day, female = 1 × 6/day), and all participants were free of illicit drug and cigarette effects at the time of scan. As GABA concentration has been shown to be affected by female ovulation (De Bondt et al., 2015), the menstrual phase of females was estimated by establishing the number of days since their last menstruation onset (high: luteal = 1, follicular = 3, hormonal contraceptive = 5, missing = 1, low: follicular = 3, ovulation = 1, hormonal contraceptive = 6). The GABA concentration of the ovulating participant was within two standard deviations of the mean GABA concentration for their group and was thus included in the analysis.

2.2. Autism schizotypy questionnaire (ASQ)

The ASQ included all items from the AQ, SPQ, Coolidge axis II inventory (CATI+) schizotypy and schizoid scales, and short Eysenck personality questionnaire revised lie scale (EPQR-L). The AQ is a 50-item assessment of autistic tendency across five dimensions: social skills, communication, attention switching, attention to detail and imagination (Baron-Cohen et al., 2001). The SPQ is a 74-item measure of schizotypal personality traits (Raine, 1991). Three superordinate dimensions encapsulate the nine sub-scales: ideas of reference, odd beliefs, unusual perceptual experiences, and suspiciousness (cognitive-perceptual features); social anxiety, no close friends and constricted affect (interpersonal features); odd behaviour and odd speech (disorganised features). The CATI+ schizotypy subscale consists of 22 items measuring odd beliefs and magical thinking, unusual perceptual experiences, suspiciousness, inappropriate or odd behaviour, and social anxiety (Coolidge and Merwin, 1992). The schizoid scale consists of 10 items assessing long term absence of social relationships, solitary activities, muted affect and withdrawal. The 12 item EPQR-L assesses social desirability and response honesty (Eysenck et al., 1985). All items

were presented on a 4-point Likert scale from 1(*strongly disagree*) to 4(*strongly agree*) (Eysenck et al., 1985). This study adopted a full-scale scoring system to provide higher item-item correlations and improve reliability (Austin, 2005; Wuthrich and Bates, 2005; Ford and Crewther, 2014). Thus, the scores on the AQ and SPQ, as analysed, yield a total out of 200 and 296, respectively.

The 168 ASQ items were presented on-line using the Opinio software interface (ObjectPlanet, 1998-2016). With the original 1678 responses, a principle axis factor analysis with promax rotation was conducted with the AQ and SPQ subscales only, using SPSS version 23.0 (IBM Corp, 2015). Following rotation, two factors yielded eigenvalues > 1; these factors were consistent with Ford and Crewther's Social Disorganisation and Perceptual Oddities factors (Ford and Crewther, 2014), respectively, and with the two principal components reported by Dinsdale et al. (2013). The full factor structure is presented in the Supplementary Information (SI) of Ford et al. (2017a). Normalised regression *z*-scores for each participant on Social Disorganisation and Perceptual Oddities were calculated, with a mean value of zero. Those with a Social Disorganisation score in the top 20% (high Social Disorganisation) and bottom 20% (low Social Disorganisation, see SI Fig. 1) were contacted to participate in the ^{1}H-MRS study, and the first 10 male and 10 female responders for each group were recruited to ensure age and sex matched groups, as well as adequate power. AQ and SPQ subscale scores for the high and low Social Disorganisation groups are presented in SI Table 1.

2.3. ^{1}H-MRS protocol

All ^{1}H-MRS and T1-weighted images were recorded from a 3T Siemens TIM Trio whole-body magnetic resonance imaging system (Erlangen, Germany) with a 32-channel head coil, at the Swinburne University Neuroimaging Facility. T1-weighted images, for ^{1}H-MRS voxel of interest localisation and tissue composition, were acquired sagittally using a magnetisation preprepared rapid gradient echo (MPRage) pulse sequence with an inversion recovery (176 slices, slice thickness = 1.0 mm, voxel resolution = 1.0 mm^3, TR = 1900 ms, TE = 2.52 ms, TI = 900 ms, bandwidth = 170 Hz /Px, flip angle = 9°, field of view 350 mm × 263 mm × 350 mm, orientation sagittal, acquisition time = 5 min).

The T1 image was used to position a 20 × 30 × 20 mm voxel in the left and the right superior temporal gyrus, encapsulating the primary auditory cortex, temporoparietal junction and part of the inferior parietal lobe (Fig. 1 (d) and SI Fig. 2). For localised glutamate quantification, an 80TE (Schubert et al., 2004) PRESS sequence was employed with chemical shift selective (CHESS) (Haase, 1986) water suppression (TR = 2000 ms, bandwidth = 1200 Hz, 80 averages, acquisition time = 2 min 48 s). Eight spectral water averages were acquired with identical PRESS parameters and shim, but with water suppression turned off.

To quantify GABA, a MEGA-PRESS (Mescher et al., 1998) editing sequence was applied with CHESS water suppression (TE = 68 ms, TR = 1500 ms, bandwidth = 1000 Hz, edit-on pulse frequency = 1.9 ppm, edit-off pulse frequency = 7.5 ppm, edit pulse bandwidth = 44 Hz, 120 averages acquired, duration = 6 min 6 s). During the edit-on sequence, a Gaussian editing pulse was centred at 1.9 ppm. The edit-on sequence was interleaved with an edit-off sequence in which a Gaussian editing pulse was centred at 7.5 ppm. The edit-off pulse at 7.5 ppm does not suppress macromolecular (MM) concentrations at 3.0 ppm, thus GABA + MM (GABA+) concentrations are reported. Twelve spectral water averages with identical MEGA-PRESS parameters were acquired with water suppression turned off. For all ^{1}H-MRS scans, an automatic shim was complemented with manual shimming until the line-width was less than 20 Hz. An example spectrum of each voxel for each group is presented in SI Fig. 3.

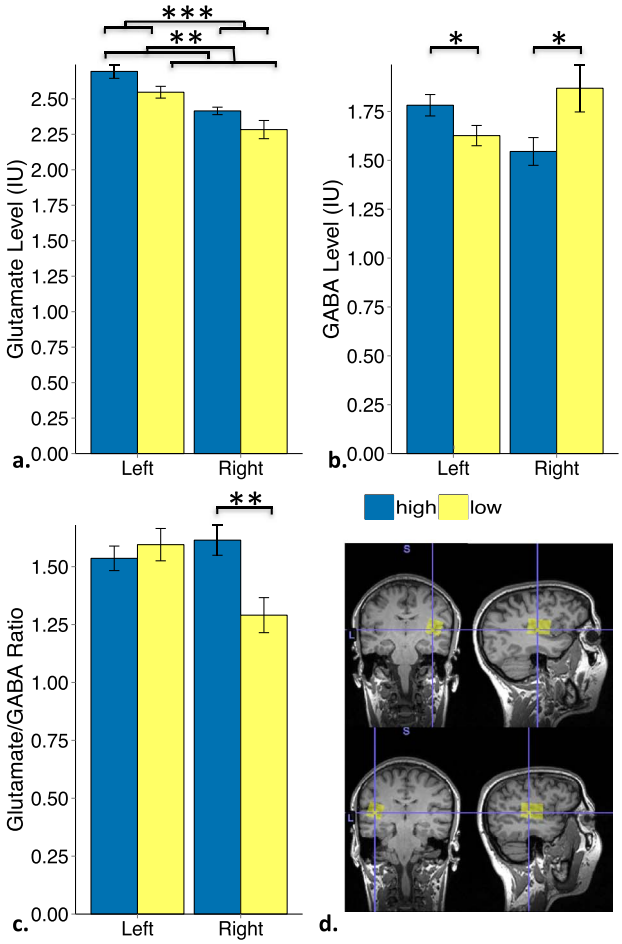

Fig. 1. Between group right and left hemisphere metabolite concentrations. High (blue) and low (yellow) Social Disorganisation group differences in (a) glutamate concentration, (b) GABA+ concentration and (c) glutamate/GABA+ ratio difference for right and left hemisphere superior temporal voxels. Means bars are presented with standard errors. (d) is an example voxel placement in the right (top) and left (bottom) superior temporal region. Note: *** < 0.001, ** < 0.025 (Bonferroni corrected alpha), * < 0.05. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.4. Analysis

Analysis of the glutamate data was conducted with TARQUIN version 4.3.7, which uses a non-negative least-squares projection of a parametrised basis set (see SI Additional methods) to estimate signal amplitude in the time-domain (Wilson et al., 2011). Eddy current correction was applied. All glutamate data had adequate fit, with signal to noise (SNR) > 20 and water line-width less than 12 Hz (see SI Table 2), although the left voxel data of participant was excluded due large water drift (water frequency SD = −6.88). No right hemisphere data was recorded for one male in the low Social Disorganisation group.

GABA+ analysis was conducted using Gannet's GABA analysis toolkit for Matlab (version 2.0), a specialised software package for GABA+ analysis (Edden et al., 2014). Gannet performs spectral registration in order to correct for frequency and phase drift (Near et al., 2015). The edit-on spectrum was subtracted from the edit-off spectrum to expose GABA+ concentration at 3.0 ppm in institutional units (IU) relative to the water spectra (Mullins et al., 2014); for a detailed description of the Gannet toolkit see Edden et al. (2014). All GABA spectra were adequate, with fit error less than 15% and creatine line-width less than 11 Hz.

There was no group or hemisphere difference in line-width, standard deviation of the water frequency, fit error or SNR for the

glutamate and GABA+ spectra, except that GABA fit error was higher on average for the left compared to the right hemisphere voxel, and line-width was larger on average in the right compared to the left hemisphere voxel (see SI Spectra Quality and Table 2). Nevertheless, fit parameters are within a normal range, and the small differences in fit error and line-width between the hemispheres are insufficient to contribute to the reported concentration of GABA+.

Glutamate and GABA+ concentrations were corrected for individual voxel tissue composition differences using the formula given by Harris et al. (2015) (see SI Additional methods). There was no difference between the groups or hemispheres in grey matter, white matter and cerebrospinal fluid (see SI Table 2).

Statistical analysis for all metabolite data was carried out using R. Data were excluded when concentrations exceeded three standard deviations from the mean ($n = 2$ low Social Disorganisation GABA+). Glutamate/GABA+ ratio was calculated and separate 2 (hemisphere) by 2 (group) mixed analyses of variance (ANOVAs) were conducted for glutamate concentration, GABA+ concentration and glutamate/GABA+ ratio, with age and handedness entered as covariates. Where interactions were significant, *post-hoc* independent samples t-tests were conducted. The critical alpha for glutamate/GABA+ ratio and the *post-hoc* independent samples t-tests were Bonferroni corrected for multiple comparisons (0.05/2 = 0.025). Omega $(\omega)^2$ and Hedges' g were calculated as less biased measure of effect size estimate of the main effect and interaction terms, and t-tests, respectively.

3. Results

^{1}H-MRS of right and left hemisphere temporal voxels revealed decreased GABA+ concentration and increased glutamate/GABA+ ratio in the right hemisphere voxel, increased left hemisphere GABA+, and slightly increased glutamate concentration bilaterally, for the high Social Disorganisation group (Fig. 1). Participant demographics and metabolite descriptives are presented in Table 1 and Table 2, respectively.

For glutamate concentration, there was a significant main effect for group ($F(1,18) = 9.71$, $p = 0.006$, $\omega^2 = 0.30$), confirming an overall increase in glutamate concentration for the high Social Disorganisation group. There was also a significant main effect for hemisphere ($F(1,33) = 37.68$, $p < 0.001$, $\omega^2 = 0.51$), with significantly more glutamate quantified in the left hemisphere voxel. There was no significant hemisphere by group interaction ($F(1,33) = 0.09$, $p = 0.772$, Fig. 1[a]).

Although there was no significant GABA+ concentration main effect for group ($F(1,18) = 1.12$, $p = 0.304$) or hemisphere ($F(1,32) = 0.02$, $p = 0.905$), there was a significant hemisphere by group interaction ($F(1,32) = 10.49$, $p = 0.003$, $\omega^2 = 0.22$).*Post-hoct*-tests confirmed significantly lower right hemisphere GABA+ concentration for the high Social Disorganisation group ($t(26.11) = -2.30$, $p = 0.03$, Hedges' $g = 0.79$). There was significantly higher GABA+ concentration in the left hemisphere ($t(32.59) = 2.06$, $p = 0.047$, Hedges' $g = 0.69$ (Table 2, Fig. 1[b]); these differences did not survive multiple comparisons correction (critical $\alpha = 0.025$).

There was no significant group ($F(1,18) = 3.45$, $p = 0.08$) or hemisphere main effect ($F(1,32) = 2.31$, $p = 0.138$) for glutamate/GABA+ ratio, however, the hemisphere by group interaction was significant ($F(1,32) = 10.01$, $p = 0.003$, $\omega^2 = 0.21$). *Post hoct*-tests confirmed significantly higher right hemisphere glutamate/GABA+ ratio for the high Social Disorganisation group ($t(32.64) = 3.24$, $p = 0.003$, Hedges' $g = 1.09$). There was no difference in left hemisphere glutamate/GABA+ ratio ($t(29.18) = -0.67$, $p = 0.506$) (Table 2, Fig. 1[c]).

Table 2
Post hoc comparisons for GABA+ concentration and glutamate/GABA+ ratio between high and low Social Disorganisation groups in the right and left superior temporal voxel.

	n	Mean (SD)	t	df	p	Hedges' g
Left Glutamate						
High	19	2.69 (0.21)				
Low	17	2.55 (0.17)				
GABA+						
High	19	1.78 (0.24)	2.06	32.59	0.047*	0.69
Low	16	1.63 (0.21)				
Glu/GABA+						
High	19	1.54 (0.23)	−0.67	29.18	0.505	0.23
Low	16	1.59 (0.28)				
Right Glutamate						
High	19	2.42 (0.12)				
Low	17	2.28 (0.26)				
GABA+						
High	19	1.55 (0.31)	−2.30	26.11	0.030*	0.79
Low	17	1.87 (0.50)				
Glu/GABA+						
High	19	1.61 (0.28)	3.24	32.64	0.003**	1.09
Low	17	1.30 (0.31)				

SD = standard deviation, df = degrees of freedom, * = $p < 0.05$, ** = $p < 0.025$ (Bonferroni corrected alpha).
Metabolite concentrations are given in institutional units.

4. Discussion

This is the first study to investigate cortical glutamate and GABA+ concentrations in the shared, non-clinical autistic and schizotypal trait phenotype, Social Disorganisation. ^{1}H-MRS was applied to right and left hemisphere superior temporal region voxels that included the auditory cortex. The findings suggest neurochemical differences between high and low reporters of Social Disorganisation. The key finding from this study was of increased glutamate/GABA+ ratio in the right, but not left, superior temporal region for the high Social Disorganisation group. Overall, glutamate concentration was increased for the higher Social Disorganisation group across the two voxels, and there was more glutamate in the left compared to the right voxel across both groups.

Increased glutamate/GABA+ ratio in the right superior temporal region for those reporting a higher degree of the Social Disorganisation trait phenotype supports theories of hyper-glutamatergia within the autism spectrum, which suggests a GAD enzyme deficit and/or a greater number of glutamate synthesising glial cells (Fatemi, 2008; Fatemi et al., 2002), and of NMDAr hypo-function within the schizophrenia spectrum (Marsman et al., 2014). Increased glutamate/GABA ratio has previously been reported in children with autism (Harada et al., 2011), while negative symptoms and poor global functioning have been associated with increased glutamatergic excitation (Egerton et al., 2012; Szulc et al., 2005).

The difference in glutamate/GABA+ ratio between the groups was driven by reduced right temporal GABA+ and an overall increase in glutamate concentrations for higher reporters of Social Disorganisation. Reduced GABA+ concentration in the auditory processing centres is in line with reports of reduced auditory cortex GABA/creatine ratio in children with autism, as well as their siblings (Rojas et al., 2014). Furthermore, frontal lobe GABA concentration has been found to be reduced in both autism and schizophrenia (Marsman et al., 2014; Harada et al., 2011). A deficit in inhibitory GABA+ may result in cortical disinhibition and, therefore, cortical over-excitation in the superior temporal region, which subsequently affects the neuronal growth and connectivity essential for normal functioning (Harada et al., 2011; Rubenstein and Merzenich, 2003).

It is important to note that glutamate concentration does not necessarily reflect the degree of excitation, as ^{1}H-MRS cannot distinguish between excitatory synaptic neurotransmitter glutamate and dormant cellular glutamate (Stagg et al., 2011). Nevertheless, Stagg et al. (2009) demonstrated a relationship between cortical excitation and glutamate concentration. Similarly, ^{1}H-MRS cannot currently distinguish between the two major pools of GABA+, therefore results reflect a reduction in the concentrations in neurotransmission and/or neuromodulatory pools of GABA+ (Stagg et al., 2011).

Excitation/inhibition balance in the auditory system is essential for appropriate auditory responding, and necessary for perceptual, cognitive and executive functions (Rubenstein and Merzenich, 2003). Over-excitation may lead to cortical instability, which significantly impacts synaptic and/or circuitry plasticity (Rubenstein and Merzenich, 2003; LeBlanc and Fagiolini, 2011). In the auditory cortex, excess excitatory/inhibitory processes may lead to hyper-reactivity or hyper-sensitivity to environmental auditory stimuli, and could be associated with deficits in the social and communication skills characteristic of the autism and schizophrenia spectra (Rossignol, 2011; Gandal et al., 2012), particularly within the Social Disorganisation phenotype. Altogether, these findings suggest that increased right temporal glutamate/GABA+ ratio in high Social Disorganisation might be related to social and interpersonal deficits, which may be representative of similar symptom characteristics across the autism and schizophrenia spectra.

The right hemisphere is involved in the processing of prosody and the paralinguistic aspects of language (Lindell, 2006), and may in part explain to the lateralisation of the glutamate/GABA+ ratio difference identified in this study. Prosody, including pitch, stress and emotion, allows for the communication of meaning though articulation. Dysfunction in right hemisphere language centres has been found to result in flattened affect (Lindell, 2006), a central feature of the Social Disorganisation trait phenotype. Damage to the right hemisphere has also been associated with difficulty in interpreting prosody and, in turn, the capacity for one to understand the emotional content of the speech of others. Furthermore, right hemisphere damage has been associated with difficulty understanding sarcasm and overly literal interpretations of proverbs, idioms and metaphors (Lindell, 2006). A glutamate/GABA+ ratio difference in this region might, therefore, have downstream effects on the interpretation and understanding of language.

There was a trend level increase in the left superior temporal voxel GABA+ concentration for the high Social Disorganisation group, suggesting that differences between groups may be lateralised. The left superior temporal voxel included Wernicke's area, the speech comprehension centre of the cortex (Lindell, 2006). Increased GABA+ might indicate increased inhibition in this region, perhaps leading to a reduction in the capacity of this region to process language.

These data also show significantly more glutamate in the left compared to right temporal voxel across both groups. To the authors' knowledge, this is the first study to identify glutamate hemispheric asymmetry in a non-clinical population. One possible explanation is that due to the left temporal dominance in speech comprehension and production (Lindell, 2006), higher regional glutamate reserves are required for efficient initial interpretation of incoming auditory information.

The significant implications of this the findings of this study are three-fold. First, these data suggest a spectrum of glutamate and GABA+ concentration differences within the non-clinical Social Disorganisation phenotype, and that these differences coincide with those reported across the autism and schizophrenia spectra. Furthermore, the group differences are unaffected by acute effects of psychiatric medications, a potential confound of much of the clinical literature (Rojas et al., 2014; Brown et al., 2013; Tebartz van Elst et al., 2014; Marsman et al., 2014).

Secondly, considering the apparent spectrum nature of neurochemical deficits, it is concerning that clinical studies rarely report trait symptoms in control samples (Ford and Crewther, 2016). Given the evidence herein, future research should incorporate trait assessments for both clinical and non-clinical samples in order to control for trait-related variability of neurochemical concentrations (Ford and Crewther, 2016).

Finally, neurochemical abnormalities may be more specific to spectrum phenotypes rather than spectrum conditions as a whole, with increased glutamate/GABA+ ratio perhaps more closely related to the Social Disorganisation phenotype. Further research into this area is therefore warranted in order to investigate the translation of these findings to the clinical population. Such research would inform pharmaceutical research into interventions that target the glutamatergic and GABAergic systems, systems that may be more effective in reducing the severity of pervasive psychosocial symptoms. Targeting the glutamatergic system early has been shown to normalise elevated glutamate concentrations and reduce symptoms severity (de la Fuente-Sandoval et al., 2013), as well as reducing the severity of cognitive decline from psychosis onset (Dempster et al., 2015). First however, specific mechanisms for abnormalities in clinical conditions must be elucidated.

Although the inclusion of those at the extreme ends of the non-clinical Social Disorganisation spectrum could be seen as a limitation, the purpose was to first establish the presence of neurochemical differences within the spectra. Furthermore, as the self-report ASQ relies on introspection and recognition of ones own social skills, by taking only the top and bottom quintiles of Social Disorganisation reporters, subjective error is accounted for. It might be expected that the high Social Disorganisation group would have a higher prevalence of an autism or schizophrenia spectrum disorder, however, considering the sample was derived from a general population and was based on a single shared domain of symptoms, it cannot be assumed that those in the high group would also meet clinical criteria for other required dimensions, such as the positive symptoms of schizophrenia and restricted and repetitive behaviours of autism. Furthermore, due to the multidimensional and spectrum nature of many brain disorders, it is possible that the Social Disorganisation phenotype is present in other psychopathologies, such as anxiety and depression. However, this does not imply that Social Disorganisation does not exist, and we suggest that the isolation of the Social Disorganisation phenotype provides a truer representation of a specific dimension that exists within the autistic and schizotypal spectra. Finally, in order to isolate auditory regions a smaller voxel was used, however, statistical analysis demonstrated clearly that, despite this smaller voxel and relatively short scan time, the group differences were robust.

4.1. Conclusion

This study demonstrates increased glutamate/GABA+ ratio for high compared to low scorers on the shared autistic and schizotypal non-clinical trait phenotype, Social Disorganisation. The difference between the groups is indicative of an abnormality that might explain some of the behaviours associated with this shared phenotype, such as social and communication difficulties. These findings have major implications for future research into the broader autism and schizophrenia spectrum disorder phenotypes, particularly the role of glutamate and GABA+. Furthermore, results highlight the need to record and report trait-related data in both experimental and control groups. In conclusion, increased glutamate/GABA+ ratio in the right auditory region may lead to behavioural and cognitive characteristics of the shared Social Disorganisation phenotype with in the autism and schizotypal spectra.

Acknowledgments

We would like to acknowledge The Swinburne Neuroimaging Department for the facilities and invaluable support for this project and Dr. Peter Goodin for the tissue segmentation script. Funding for this study was provided by a Swinburne University Neuroimaging GrantandThe National Health and Medical Research Council of Australia,APP1004740.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2017.07.009.

References

Arthur, W.W., Day, D.V.D.V., 1994. Development of a short form for the raven advanced progressive matrices test. Educ. Psychol. Meas. 54 (2), 394–403.

Austin, E.J.E.J., 2005. Personality correlates of the broader autism phenotype as assessed by the autism spectrum quotient (AQ). Personal. Individ. Differ. 38, 451–460. http://dx.doi.org/10.1016/j.paid.2004.04.022.

Bak, L.K.L.K., Schousboe, A.A., Waagepetersen, H.S.H.S., 2006. The glutamate/GABA-glutamine cycle: aspects of transport, neurotransmitter homeostasis and ammonia transfer. J. Neurochem. 98 (3), 641–653. http://dx.doi.org/10.1111/j.1471-4159.2006.03913.x.

Baron-Cohen, S.S., Wheelwright, S.S., Skinner, R.R., Martin, J.J., Clubley, E.E., 2001. The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. J. Autism Dev. Disord. 31 (1), 5–17. http://dx.doi.org/10.1023/A:1005653411471.

Brown, M.S.M.S., Singel, D.D., Hepburn, S.S., Rojas, D.C.D.C., 2013. Increased glutamate concentration in the auditory cortex of persons with autism and first-degree relatives: a ^{1}H-MRS study. Autism Res. 6 (1), 1–10. http://dx.doi.org/10.1002/aur.1260.

Coghlan, S.S., Horder, J.J., Inkster, B.B., Mendez, M.A.M.A., Murphy, D.G.D.G., Nutt, D.J.D.J., 2012. GABA system dysfunction in autism and related disorders: from synapse to symptoms. Neurosci. Biobehav. Rev. 36 (9), 2044–2055. http://dx.doi.org/10.1016/j.neubiorev.2012.07.005.

Coolidge, F.L.F.L., Merwin, M.M.M.M., 1992. Reliability and validity of the Coolidge Axis II Inventory: a new inventory for the assessment of personality disorders. J. Pers. Assess. 52 (2), 223–238.

Danbolt, N.C.N.C., 2001. Glutamate uptake. Prog. Neurobiol. 65 (1), 1–105. http://dx.doi.org/10.1016/S0301-0082(00)00067-8.

De Bondt, T.T., De Belder, F.F., Vanhevel, F.F., Jacquemyn, Y.Y., Parizel, P.M.P.M., 2015, 2. Prefrontal GABA concentration changes in women–influence of menstrual cycle phase, hormonal contraceptive use, and correlation with premenstrual symptoms. Brain Res. 1597, 129–138. http://dx.doi.org/10.1016/j.brainres.2014.11.051.

de la Fuente-Sandoval, C.C., Leon-Ortiz, P.P., Azcarraga, M.M., Stephano, S.S., Favila, R.R., Diaz-Galvis, L.L., et al., 2013. Glutamate levels in the associative striatum before and after 4 weeks of antipsychotic treatment in first-episode psychosis: a longitudinal proton magnetic resonance spectroscopy study. JAMA Psych. 70 (10), 1057–1066. http://dx.doi.org/10.1001/jamapsychiatry.2013.289.

Dempster, K.K., Norman, R.R., Theberge, J.J., Densmore, M.M., Schaefer, B.B., Williamson, P.P., 2015. Glutamatergic metabolite correlations with neuropsychological tests in first episode schizophrenia. Psych. Res. 233 (2), 180–185. http://dx.doi.org/10.1016/j.pscychresns.2015.06.003.

Dinsdale, N.L.N.L., Hurd, P.L.P.L., Wakayabashi, A.A., Elliot, M.M., Crespi, B.J.B.J., 2013. How are autism and schizotypy related? Evidence from a non-clinical population. PLoS ONE 8 (5), 1–10. http://dx.doi.org/10.1371/journal.pone.0063316.

Edden, R.A.E.R.A.E., Puts, N.A.J.N.A.J., Harris, A.D.A.D., Barker, P.B.P.B., Evans, C.J.C.J., 2014. Gannet: a batch-processing tool for the quantitative analysis of gamma-aminobutyric acid-edited MR spectroscopy spectra. J. Magn. Reson. Imaging 40 (6), 1445–1452. http://dx.doi.org/10.1002/jmri.24478.

Egerton, A.A., Brugger, S.S., Raffin, M.M., Barker, G.J.G.J., Lythgoe, D.J.D.J., McGuire, P.K.P.K., et al., 2012. Anterior cingulate glutamate levels related to clinical status following treatment in first-episode schizophrenia. Neuropsychopharmacology 37 (11), 2515–2521. http://dx.doi.org/10.1038/npp.2012.113.

Eysenck, S.S., Eysenck, H.H., Barrett, P.P., 1985. A revised version of the psychoticism scale. Personal. Individ. Differ. 6 (1), 21–29. http://dx.doi.org/10.1016/0191-8869(85)90026-1.

Fatemi, S.S., Halt, A.R.A.R., Stary, J.M.J.M., Kanodia, R.R., Schulz, S.S., Realmuto, G.R.G.R., 2002. Glutamic acid decarboxylase 65 and 67 kDa proteins are reduced in autistic parietal and cerebellar cortices. Biol. Psychiatry 52 (8), 805–810. http://dx.doi.org/10.1016/S0006-3223(02)01430-0.

Fatemi, S.S., Reutiman, T.T., Folsom, T.T., Thuras, P.P., 2009. GABAA receptor down-regulation in brains of subjects with autism. J. Autism Dev. Disord. 39 (2), 223–230. http://dx.doi.org/10.1007/s10803-008-0646-7.

Fatemi, S.H.S.H., 2008. The hyperglutamatergic hypothesis of autism. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 32 (3), 911. http://dx.doi.org/10.1016/j.pnpbp.2007.11.004.

Ford, T.C.T.C., Crewther, D.P.D.P., 2014. Factor analysis demonstrates a common schizoidal phenotype within autistic and schizotypal tendency: implications for neuroscientific studies. Front. Psych. 5 (117). http://dx.doi.org/10.3389/fpsyt.2014.00117.

Ford, T.C.T.C., Crewther, D.P.D.P., 2016. A comprehensive review of the ^{1}H-MRS metabolite spectrum in autism spectrum disorder. Front. Mol. Neurosci. 9 (14). http://dx.doi.org/10.3389/fnmol.2016.00014.

Ford, T.C.T.C., Woods, W.W., Crewther, D.P.D.P., 2017a. Mismatch field latency, but not power, may mark a shared autistic and schizotypal trait phenotype. Int. J. Psychiatry 116, 60–67. http://dx.doi.org/10.1016/j.ijpsycho.2017.02.008.

Ford, T.C.T.C., Woods, W.W., Crewther, D.P.D.P., 2017b. Spatio-temporal source cluster analysis reveals fronto-temporal auditory change processing differences within a shared autistic and schizotypal trait phenotype. NeuroImage: Clinical. http://dx.doi.org/10.1016/j.nicl.2017.04.022.

Fulham, W.R.W.R., Michie, P.T.P.T., Ward, P.B.P.B., Rasser, P.E.P.E., Todd, J.J., Johnston, P.J.P.J., et al., 2014. Mismatch negativity in recent-onset and chronic schizophrenia: a current source density analysis. PLoS One 9 (6), e100221. http://dx.doi.org/10.1371/journal.pone.0100221.

Gandal, M.J.M.J., Anderson, R.L.R.L., Billingslea, E.N.E.N., Carlson, G.C.G.C., Roberts, T.P.T.P., Siegel, S.J.S.J., 2012. Mice with reduced NMDA receptor expression: more consistent with autism than schizophrenia? Genes Brain Behav. 11 (6), 740-50. http://dx.doi.org/10.1111/j.1601-183X.2012.00816.x.

Haase, A.A., 1986. Localization of unaffected spins in NMR imaging and spectroscopy (LOCUS spectroscopy). Magn. Reson. Med. 3 (6), 963–969. http://dx.doi.org/10.1002/mrm.1910030619.

Harada, M.M., Taki, M.M.M.M., Nose, A.A., Kubo, H.H., Mori, K.K., Nishitani, H.H., et al., 2011. Non-invasive evaluation of the GABAergic/glutamatergic system in autistic patients observed by MEGA-editing proton MR spectroscopy using a clinical 3 tesla instrument. J. Autism Dev. Disord. 41 (4), 447–454. http://dx.doi.org/10.1007/s10803-010-1065-0.

Harris, A.D.A.D., Puts, N.A.J.N.A.J., Edden, R.A.E.R.A.E., 2015. Tissue correction for GABA-edited MRS: considerations of voxel composition, tissue segmentation, and tissue relaxations. J. Magn. Reson. Imaging 42 (5), 1431–1440. http://dx.doi.org/10.1002/jmri.24903.

Horder, J.J., Lavender, T.T., Mendez, M.A.M.A., O'Gorman, R.R., Daly, E.E., Craig, M.C.M.C., et al., 2013. Reduced subcortical glutamate/glutamine in adults with autism spectrum disorders: a ^{1}H-MRS study. Transl. Psychiatry 3, e279. http://dx.doi.org/10.1038/tp.2013.53.

Corp, I.B.M.I.B.M., 2015. IBM SPSS Statistics for Macintosh. IBM Corp, 23.0 ed. Armonk, NY.

Juchem, C.C., Rothman, D.L.D.L., 2014. Chapter 1.1 — basis of magnetic resonance. In: Stagg, C.C., Rothman, D.L.D.L. (Eds.), Magnetic Resonance Spectroscopy. Academic Press, San Diego, pp. 3–14. http://dx.doi.org/10.1016/B978-0-12-401688-0.00001-X. ISBN 978-0-12-401688-0.

Kantrowitz, J.T.J.T., Javitt, D.C.D.C., 2010. *N*-methyl-D-aspartate (NMDA) receptor dysfunction or dysregulation: the final common pathway on the road to schizophrenia? Brain Res. Bull. 83 (3-4), 108–121. http://dx.doi.org/10.1016/j.brainresbull.2010.04.006.

Kompus, K.K., Westerhausen, R.R., Craven, A.R.A.R., Kreegipuu, K.K., Põldver, N.N., Passow, S.S., et al., 2015. Resting-state glutamatergic neurotransmission is related to the peak latency of the auditory mismatch negativity (MMN) for duration deviants: an ^{1}H-MRS-EEG study. Psychophysiology 52 (9), 1131–1139. http://dx.doi.org/10.1111/psyp.12445.

LeBlanc, J.J.J.J., Fagiolini, M.M., 2011. Autism: A "critical period" disorder? Neural Plast. 2011, 1–17. http://dx.doi.org/10.1155/2011/921680.

Lindell, A.K.A.K., 2006. In your right mind: right hemisphere contributions to language processing and production. Neuropsychol. Rev. 16 (3), 131–148. http://dx.doi.org/10.1007/s11065-006-9011-9.

Lisman, J.E.J.E., Coyle, J.T.J.T., Green, R.W.R.W., Javitt, D.C.D.C., Benes, F.M.F.M., Heckers, S.S., et al., 2008. Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. Trends Neurosci. 31 (5), 234–242. http://dx.doi.org/10.1016/j.tins.2008.02.005.

Marsman, A.A., Mandl, R.C.W.R.C.W., Klomp, D.W.J.D.W.J., Bohlken, M.M.M.M., Boer, V.O.V.O., Andreychenko, A.A., et al., 2014. GABA and glutamate in schizophrenia: a 7T ^{1}H-MRS study. NeuroImage 6, 398–407. http://dx.doi.org/10.1016/j.nicl.2014.10.005.

Marsman, A.A., van den Heuvel, M.P.M.P., Klomp, D.W.J.D.W.J., Kahn, R.S.R.S., Luijten, P.R.P.R., Hulshoff Pol, H.E.H.E., 2013. Glutamate in schizophrenia: a focused review and meta-analysis of ^{1}H-MRS studies. Schizophrenia Bulletin 39 (1), 120–129. http://dx.doi.org/10.1093/schbul/sbr069.

McKenna, M.C.M.C., 2007. The glutamate–glutamine cycle is not stoichiometric: fates of glutamate in brain. J. Neutron Res. 85 (15), 3347–3358. http://dx.doi.org/10.1002/jnr.21444.

McKenna, M.C.M.C., Gruetter, R.R., Sonnerwald, U.U., Waagepetersen, H.S.H.S., Schousboe, A.A., 2011. Principles of Molecular, Cellular, and Medical Neurobiology. In: Basic Neurochemistry, 8 ed. Elsevier Academic Press, New York, pp. 200–230. http://dx.doi.org/10.1002/jnr.21444. chap. 11.

Mescher, M.M., Merkle, H.H., Kirsch, J.J., Garwood, M.M., Gruetter, R.R., 1998. Simultaneous in vivo spectral editing and water suppression. NMR Biomed. 11 (6), 266–272. http://dx.doi.org/10.1002/(SICI)1099-1492(199810)11:6<266::AID-NBM530>3.0.CO;2-J.

Mullins, P.G.P.G., McGonigle, D.J.D.J., O'Gorman, R.L.R.L., Puts, N.A.N.A., Vidyasagar, R.R., Evans, C.J.C.J., et al., 2014. Current practice in the use of MEGA-PRESS spectroscopy for the detection of GABA. Neuroimage 86, 43–52. http://dx.doi.org/10.1016/j.neuroimage.2012.12.004.

Near, J.J., Edden, R.R., Evans, C.J.C.J., Paquin, R.R., Harris, A.A., Jezzard, P.P., 2015. Frequency and phase drift correction of magnetic resonance spectroscopy data by spectral registration in the time domain. Magn. Reson. Med. 73 (1), 44–50. http://dx.doi.org/10.1002/mrm.25094.

ObjectPlanet, 1998-2016. Opinio 6.8.2. http://www.objectplanet.com/opinio/.

Pinkham, A.E.A.E., Hopfinger, J.B.J.B., Pelphrey, K.A.K.A., Piven, J.J., Penn, D.L.D.L., 2008. Neural bases for impaired social cognition in schizophrenia and autism spectrum disorders. Schizophr. Res. 99 (1-3), 164–175. http://dx.doi.org/10.1016/j.schres.2007.10.024.

Raine, A.A., 1991. The SPQ- a scale for the assessment of schizotypal personality based on DSM-III-R criteria. Schizophr. Bull. 17 (4), 555–564. http://dx.doi.org/10.1093/schbul/17.4.555.

Rasser, P.E.P.E., Schall, U.U., Todd, J.J., Michie, P.T.P.T., Ward, P.B.P.B., Johnston, P.P., et al., 2011. Gray matter deficits, mismatch negativity, and outcomes in schizophrenia. Schizophr. Bull. 37 (1), 131–140. http://dx.doi.org/10.1093/schbul/sbp060.

Robertson, C.E.C.E., Ratai, E.-M.E.-M., Kanwisher, N.N., 2016, 2016/05/15. Reduced GABAergic action in the autistic brain. Curr. Biol. 26 (1), 80–85. http://dx.doi.org/10.1016/j.cub.2015.11.019.

Rojas, D.C.D.C., Singel, D.D., Steinmetz, S.S., Hepburn, S.S., Brown, M.S.M.S., 2014. Decreased left perisylvian GABA concentration in children with autism and unaffected siblings. NeuroImage 86, 28–34. http://dx.doi.org/10.1016/j.neuroimage.

2013.01.045.
Rossignol, E.E., 2011. Genetics and function of neocortical GABAergic interneurons in neurodevelopmental disorders. Neural Plast. 2011, 1–25. http://dx.doi.org/10.1038/mp.2010.136.
Rubenstein, J.L.R.J.L.R., Merzenich, M.M.M.M., 2003. Model of autism: increased ratio of excitation/ inhibition in key neural systems. Genes Brain Behav. 2, 255–267. http://dx.doi.org/10.1046/j.1601-183X.2003.00037.x.
Schubert, F.F., Gallinat, J.J., Seifert, F.F., Rinneberg, H.H., 2004. Glutamate concentrations in human brain using single voxel proton magnetic resonance spectroscopy at 3 tesla. NeuroImage 21 (4), 1762–1771. http://dx.doi.org/10.1016/j.neuroimage.2003.11.014.
Spek, A.A.A.A., Wouters, S.G.M.S.G.M., 2010. Autism and schizophrenia in high functioning adults: behavioral differences and overlap. Res. Autism Spect. Disord. 4, 709–717. http://dx.doi.org/10.1016/j.rasd.2010.01.009.
Stagg, C.J.C.J., Bachtiar, V.V., Johansen-Berg, H.H., 2011. What are we measuring with GABA magnetic resonance spectroscopy? Commun. Integr. Biol. 4 (5), 573–575. http://dx.doi.org/10.4161/cib.4.5.16213 10.1016/j.cub.2011.01.069.
Stagg, C.J.C.J., Best, J.G.J.G., Stephenson, M.C.M.C., O'Shea, J.J., Wylezinska, M.M., Kincses, Z.T.Z.T., et al., 2009. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J. Neurosci. 29 (16), 5202–5206. http://dx.doi.org/10.1523/JNEUROSCI.4432-08.2009.
Sugranyes, G.G., Kyriakopoulos, M.M., Corrigall, R.R., Taylor, E.E., Frangou, S.S., 2011. Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition. PLoS One 6 (10), 1–13. http://dx.doi.org/10.1371/journal.pone.0025322.
Szulc, A.A., Galinska, B.B., Tarasow, E.E., Dzienis, W.W., Kubas, B.B., Konarzewska, J.J., et al., 2005. The effect of risperidone on metabolite measures in schizophrenic patients. A proton magnetic resonance spectroscopy (^{1}H-MRS) study. Pharmacopsychiatry 38, 214–219. http://dx.doi.org/10.1055/s-2005-873156.
Tebartz van Elst, L.L., Maier, S.S., Fangmeier, T.T., Endres, D.D., Mueller, G.T.G.T., Nickel, K.K., et al., 2014. Disturbed cingulate glutamate metabolism in adults with high-functioning autism spectrum disorder: evidence in support of the excitatory/inhibitory imbalance hypothesis. Mol. Psychiatry 19 (12), 1314–1325. http://dx.doi.org/10.1038/mp.2014.62.
Wilson, M.M., Reynolds, G.G., Kauppinen, R.A.R.A., Arvanitis, T.N.T.N., Peet, A.C.A.C., 2011. A constrained least-squares approach to the automated quantitation of in vivo (1)H magnetic resonance spectroscopy data. Magn. Reson. Med. 65 (1), 1–12. http://dx.doi.org/10.1002/mrm.22579.
Wuthrich, V.V., Bates, T.C.T.C., 2005. Reliability and validity of two Likert versions of the schizotypal personality questionnaire (SPQ). Personal. Individ. Differ. 38 (7), 1543–1548. http://dx.doi.org/10.1016/j.paid.2004.09.017.
Yizhar, O.O., Fenno, L.E.L.E., Prigge, M.M., Schneider, F.F., Davidson, T.J.T.J., O'Shea, D.J.D.J., et al., 2011. Neocortical excitation/inhibition balance in information processing and social dysfunction. Nature 477 (7363), 171–178. http://dx.doi.org/10.1038/nature10360.