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The association of excitation and inhibition signaling with the relative symptom expression of autism and psychosis-proneness: Implications for psychopharmacology

Talitha C. Ford[a,*], Ahmad Abu-Akel[b], David P. Crewther[a]

[a] Centre for Human Psychopharmacology, Arts and Design, Swinburne University of Technology, Melbourne, Victoria, Australia
[b] Institute of Psychology, University of Lausanne, Lausanne, Switzerland

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ABSTRACT

The underlying mechanisms of autism and schizophrenia are poorly understood, partly due to a lack of dimension-specific research. Aberrant excitatory and inhibitory neurotransmission are implicated in both conditions, particularly in social dysfunction. This study investigates the extent to which the degree of autistic tendency and psychosis-proneness exclusively and interactively predict excitatory and inhibitory neurotransmitter concentrations in the superior temporal cortex (STC). In 38 adults (18 male, 18–40 years), we obtained autistic tendencies (Autism-Spectrum Quotient [AQ]) and psychosis-proneness scores (Schizotypal Personality Questionnaire [PP]); magnetic resonance spectroscopy (MRS) quantified glutamate and GABA+ concentrations from the STC. Results demonstrated a negative AQ/PP interaction with glutamate concentration for the left STC voxel, where PP increased with glutamate for average AQ, while AQ decreased with glutamate for average-high PP. There was a negative AQ/PP interaction with glutamate/GABA+ ratio for the right STC, AQ increasing with glutamate/GABA+ for low-average PP, while PP decreased with glutamate/GABA+ for high AQ. Consistent with animal studies, we also reveal that overall reduced glutamate/GABA+ ratio might be precipitated by increased right hemisphere GABA+ concentrations. These findings illustrate the importance of considering the concurrent effects of autism and psychosis dimensions on understanding the pathophysiological mechanisms implicated in either condition, and can advance psychopharmacological research into better treatment options for patients.

1. Introduction

Autism and schizophrenia spectrum conditions exhibit many behavioral, socio-cognitive and neurological similarities. However, the two conditions remain diagnostically distinct. The underlying mechanisms of their similarities and differences are poorly understood due to a lack of dimension-specific research, and the confounding effects of psychiatric medications, illness duration and acute symptomatology that affect cognitive, behavioral and neural outcomes (Insel, 2010; Stefansson et al., 2014). It is well established that autism and schizophrenia are spectrum disorders, with their symptom traits expressed across the subclinical population (Baron-Cohen et al., 2001; Ford and Crewther, 2014; Raine, 1991; Spek and Wouters, 2010). Investigating the healthy populations can be important in providing insights on how these dimension traits can affect condition-specific phenotypes. This study investigates the extent to which co-occurring autistic and psychosis tendencies exclusively and interactively predict excitatory and inhibitory neurotransmitter concentrations, in the social region of the bilateral superior temporal cortices (Deen et al., 2015).

More recently, attention has been directed to the hyper-glutamatergic hypothesis of psychosis and autism, and the hypo-GABAergic hypothesis of autism, implicating aberrant NMDAr and $GABA_A$ receptors, respectively (Cellot and Cherubini, 2014; Fatemi, 2008; Fatemi et al., 2002; Moghaddam and Javitt, 2012; Olloquequi et al., 2018). Imbalance in the relative expression of glutamatergic to GABAergic processes reflects the modulation of cortical excitatory and inhibitory processes, leading to an excitation/inhibition imbalance, which, in turn, affects neural signaling and transmission, and thus the behavioral and socio-cognitive functions that the neural systems support. Although there are no studies directly comparing excitation/inhibition between them, increased excitation/inhibition has been implicated across the autism (Canitano and Pallagrosi, 2017; Cellot and Cherubini, 2014;

* Corresponding author at: Centre for Human Psychopharmacology, Arts and Design, Swinburne University of Technology, Mailbox 71, Mail H24, PO Box 21 8, Hawthorn, Victoria 3122, Australia.
E-mail address: tcford@swin.edu.au (T.C. Ford).

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Ford and Crewther, 2016) and schizophrenia spectra (Guidotti et al., 2005). Increased excitation/inhibition has also been associated with psychotic symptoms, negative symptoms (Merritt et al., 2013) and social dysfunction (Han et al., 2014; Yizhar et al., 2011) in nonclinical studies. In fact, a recent review implicated excitotoxicity in the pathogenesis of autism and schizophrenia, suggesting it to be a key mechanism in the onset and neuroanatomical changes associated with the conditions (Olloquequi et al., 2018), while the NMDAr antagonist memantine has been shown to reduce the severity of autistic symptoms and the negative symptoms of schizophrenia (see Olloquequi et al., 2018).

Auditory processes, such as the mismatch negativity (MMN), that are governed by the modulation of excitation/inhibition through NMDAr functionality, have also been implicated in both autism (Korpilahti et al., 2007) and schizophrenia (Moghaddam and Javitt, 2012), and in social functioning (Korpilahti et al., 2007). Furthermore, reduced glutamate concentration in the auditory cortex has been reported in autism (Brown et al., 2013). These studies provide compelling evidence that an increase in the glutamate/GABA ratio, perhaps particularly in auditory processing regions, may manifest behaviorally through social difficulties. This has been illustrated in several neuroimaging studies that isolate a shared sub-clinical autistic and schizotypal trait phenotype of Social Disorganization, and demonstrate differences in auditory processing, as well as in glutamate and GABA neurotransmitter concentrations, for those with high compared to low expression of the phenotype (Ford et al., 2017a; Ford et al., 2017b; Ford et al., 2017c; Ford et al., 2017d; Ford et al., 2018). Of note, high expression of socio-cognitive difficulties have been associated with a higher glutamate/GABA ratio in the right superior temporal lobe (Ford et al., 2017a; Ford et al., 2017b), and reduced grey matter has been reported in the superior temporal regions of adults with autism, which was particularly evident for those with comorbid psychosis compared to those without (Toal et al., 2009). The right hemisphere is specialized in the processing of prosody and the paralinguistic aspects of language (Ford et al., 2017b; Lindell, 2006), so neurotransmitter alterations here may affect the interpretation of the social nuances of language, leading to socio-cognitive difficulties (Ford et al., 2017b).

It is important to note that, to date, research concerned with the excitation/inhibition hypothesis of autism and schizophrenia has either focused on the conditions separately (Canitano and Pallagrosi, 2017; Ford and Crewther, 2016; Guidotti et al., 2005), or on the overlap and similarities between these two conditions (Ford et al., 2017a; Ford et al., 2017b; Ford et al., 2017c; Ford et al., 2017d; Ford et al., 2018; Gao and Penzes, 2015). The latter approach is primarily motivated by seeming similarities in performance across these two spectra observed on various executive, attentional and socio-cognitive functions (Abu-Akel et al., 2017a; Abu-Akel et al., 2018; Spek and Wouters, 2010). However, in considering the relationship between autism and schizophrenia spectrum disorders, two emerging lines of evidence ought also to be considered: (1) that these conditions can co-occur at both the diagnostic and trait levels than would be expected by chance (Chisholm et al., 2015; Larson et al., 2017), and (2) that these conditions are at the opposite extremes of the same cognitive continuum (Abu-Akel and Bailey, 2000; Crespi and Badcock, 2008). In light of these lines of evidence, several investigations have examined the impact that such co-occurrence could have on social cognition and behavior in both healthy (Abu-Akel et al., 2017b; Abu-Akel et al., 2015) and clinical populations (Abu-Akel et al., 2017c; Abu-Akel et al., 2018; Upthegrove et al., 2017). This body of research showed that attentional, socio-cognitive and functional outcome measures are largely interactively modulated by the relative expression of autism vis-à-vis psychosis-proneness. Two recent studies have also examined the concurrent effect of these two phenotypes on neuronal activity while performing socio-cognitive tasks. At the trait level, autistic tendency and psychosis-proneness of healthy participants were interactively related to activity in the right temporo-parietal junction (TPJ) — a region central to mentalization and attention-orientation processes (Abu-Akel et al., 2017a). At the diagnostic level, adults with comorbid autism and schizotypal personality disorder activated social brain regions similarly to healthy controls during a social judgment task, and were intermediate to the groups with either disorder alone (Stanfield et al., 2017).

Taken together, these findings demonstrate that investigating autism and schizophrenia independently provides an incomplete picture of the underlying mechanisms of these disorders, such that the nature of the association of glutamate and GABA concentrations with co-occurring autistic tendency and psychosis-proneness remains unknown. Thus, the current study investigated the interactive relationship between co-occurring autistic tendency and psychosis-proneness, and glutamate, GABA and the glutamate/GABA ratio. Given that the superior temporal regions have been associated with social language nuances (Deen et al., 2015), and social deficits (Ford et al., 2017b), and that the TPJ is implicated in interactive effects of autistic tendency and psychosis-proneness on socio-cognitive processing (Abu-Akel et al., 2015), it was predicted that the interaction between autistic and psychosis-proneness would be associated with glutamate and GABA concentrations, as well as the glutamate/GABA ratio, in the superior temporal region.

2. Experimental procedures

Ethics approval was granted by the Swinburne University Human Research Ethics Committee (2011/033 Series C(d)), in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants provided written informed consent before commencing the study.

2.1. Participants

Participant recruitment and experimental group classification have been reported elsewhere (Ford and Crewther, 2014; Ford et al., 2017b). Briefly, 1678 participants (428 male, 1250 females, age 18–40) completed an online version of the Autism-Spectrum Quotient (AQ) and Schizotypal Personality Questionnaire (SPQ) via Opinio. Exploratory factor analysis of all AQ and SPQ subscales revealed the Social Disorganization factor (Ford and Crewther, 2014), and participants' standardized z-scores for Social Disorganization were calculated. Participants with a Social Disorganization score in the top (*High Social Disorganization*) and bottom (*Low Social Disorganization*) 20% were contacted to take part in the follow-up ^{1}H-MRS study. The first 10 male and 10 female responders for each group were recruited to ensure age and sex matched groups. In total, 37 participants took part in the ^{1}H-MRS study: 19 high in Social Disorganization (9 female) and 18 low in Social Disorganization (10 female).

No participants in the low group, and five participants in the high group reported a previous psychiatric condition (3 depression, 1 bipolar, 1 anorexia). No participant reported a history of autism or schizophrenia, and none were affected by a psychiatric condition at the time of the study. Participants were excluded if they were currently taking psychoactive medications, and all participants were free of illicit drug and cigarette effects at the time of scan.

2.2. Materials

The AQ is a 50-item assessment of autistic tendency with five subscales: social skill, 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 nine SPQ subscales: ideas of reference, odd beliefs, unusual perceptual experiences, and suspiciousness (cognitive-perceptual features); social anxiety, no close friends and constricted affect (interpersonal features); odd behavior and odd speech (disorganized features). All AQ and SPQ items were presented on a 4-