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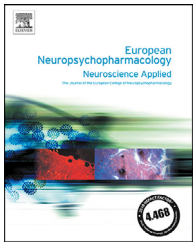

Glutamatergic function in a genetic high-risk group for psychosis: A proton magnetic resonance spectroscopy study in individuals with 22q11.2 deletion

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Abstract
Glutamatergic dysregulation is one of the leading theories regarding the pathoaetiology of schizophrenia. Meta-analysis of magnetic resonance spectroscopy studies in schizophrenia shows increased levels of glutamate and glutamine (Glx) in the medial frontal cortex and basal ganglia in clinical high-risk groups for psychosis and increased glutamine levels in the thalamus, but it is unclear if this is also the case in people at genetic high risk for psychosis. The aim of this study was to investigate glutamatergic function in the anterior cingulate cortex, striatum and thalamus in carriers of a genetic variant (22q11.2 deletion) associated with a high risk for psychosis. 53 volunteers (23 22q11.2 deletion carriers and 30 controls) underwent proton

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magnetic resonance spectroscopy imaging and neuropsychological assessments for prodromal psychotic symptoms, schizotypy, anxiety, depression and FSIQ. We did not find any difference between groups in Glx in the anterior cingulate cortex, striatum or thalamus (Glx: t(50)=-1.26, $p = 0.21$; $U = 251$, $z = -0.7$, $p = 0.49$; $U = 316$, z= -0.26, $p = 0.79$, respectively). No correlation was detected between Glx levels in any region and symptomatology or FSIQ. Our findings indicate that glutamatergic function is not altered in people at genetic high risk of psychosis due to the 22q11.2 deletion, which could suggest that this is not the mechanism underlying psychosis risk in 22q11.2 deletion carriers.

1. Introduction

Converging evidence implicates glutamatergic dysregulation in the pathophysiology of schizophrenia (Olney and Farber, 1995). This includes findings from a recent genome-wide-association study, which showed a significant association between several genes related to glutamate neurotransmission and schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics et al., 2014) and that drugs acting on the glutamate system can both induce schizophreniform symptoms in healthy volunteers (Krystal et al., 1994), and also worsen symptoms in patients with schizophrenia (Lahti et al., 1995).

Glutamate and related metabolite levels in the brain can be measured in vivo using proton Magnetic Resonance Spectroscopy (MRS). Over the last two decades, there has been a growing number of spectroscopy studies in clinical high-risk groups for psychosis (CHR) and individuals with schizophrenia (Marsman et al., 2013; Merritt et al., 2016; Poels et al., 2014), with the medial frontal cortex (including the anterior cingulate cortex (ACC)), basal ganglia and thalamus being amongst the brain regions of main interest. Results in the medial frontal cortex in people at CHR or with first episode psychosis have been conflicting, with some studies showing increased levels of glutamate and its metabolite, glutamine (collectively termed Glx) (Egerton et al., 2012; Theberge et al., 2002; Tibbo et al., 2013), whereas others have found no alterations in Glx (Egerton et al., 2018; Goto et al., 2012; Natsubori et al., 2014). Similarly, findings in the thalamus have been inconsistent (Bustillo et al., 2010; Egerton et al., 2014; Theberge et al., 2002). In contrast, previous studies in the basal ganglia both in CHR (de la Fuente-Sandoval et al., 2011, 2015) and first episode psychosis (de la Fuente-Sandoval et al., 2013, 2011; Goto et al., 2012) have consistently shown an increase in Glx.

The evidence for an association between genetic variants involved in glutamate neurotransmission with schizophrenia indicates that altered glutamate neurotransmission may be seen in people at genetic risk for psychosis. Seven MRS studies have investigated glutamate and related metabolites in the ACC, striatum and/or thalamus in groups at high familial risk for psychosis, with inconsistent results (Keshavan et al., 2009; Lutkenhoff et al., 2010; Purdon et al., 2008; Tandon et al., 2013; Thakkar et al., 2017; Treen et al., 2016; Yoo et al., 2009). These disparate findings could be because some cases of schizophrenia arise due to de novo mutations (Purcell et al., 2014) coupled with the fact that first degree relatives are discordant for about 50% of genes (Lichtenstein et al., 2009). Thus, family members included in these studies may carry few, or even no, genetic risk variants for schizophrenia.

A deletion of 1.5 to 3Mb at chromosome 22q11.2 is the most common microdeletion in humans with an estimated prevalence between 1:2000 to 1:4000 births (Fung et al., 2015; McDonald-McGinn et al., 2015). Over the last twenty-five years, it has been well established that 22q11.2 deletion increases the risk for developing psychosis by 25%–30% (Monks et al., 2014; Murphy et al., 1999). Moreover, a recent large, multicentre study in individuals carrying the 22q11.2 deletion reported that the prevalence of any schizophreniform disorder was greater than 40% in adults above the age of 26 years old (Schneider et al., 2014), making this deletion one of the strongest genetic risk factors for developing schizophrenia or a related disorder. About 10%–12% of individuals carrying this genetic mutation have a 1.5 Mb region deleted, covering about 35 genes, whilst the remainder carry a deletion spanning a 3Mb region, which encompasses 60 genes (Carlson et al., 1997; Shaikh et al., 2000). In either case, the deletion includes a gene encoding for the proline dehydrogenenase (*PRODH*), the enzyme that catalyzes the first step in the catabolism of proline (Mitsubuchi et al., 2008). In preclinical studies, L-proline has been found to have modulatory role on glutamatergic neurotransmission acting via NMDA receptors (Cohen and Nadler, 1997). Notably, hyperprolinaemia is a common finding in approximately 37%–50% of individuals with 22q11.2 deletion (Goodman et al., 2000) (Raux et al., 2007) and has been associated with cognitive deficits and psychosis (Raux et al., 2007). Similarly, genetic variation in *PRODH* has been linked with elevated proline levels and psychosis (Liu et al., 2002). Thus, it has been suggested that reduced PRODH activity in 22q11.2 deletion can lead to increased levels of proline and subsequently to changes in brain function and physiology. However, to date, no spectroscopy study has investigated glutamatergic function in the ACC, striatum or thalamus in 22q11.2 deletion.

The primary aim of our study was thus to investigate glutamatergic function in the ACC, striatum and thalamus in individuals carrying the 22q11.2 deletion. In view of the evidence discussed above we hypothesised that Glx levels would be raised in individuals with 22q11.2 deletion compared to healthy controls. A secondary aim was to examine if there was any association between glutamatergic function and symptomatology, and we hypothesised that Glx levels would be positively correlated with sub-clinical psychotic symptoms.

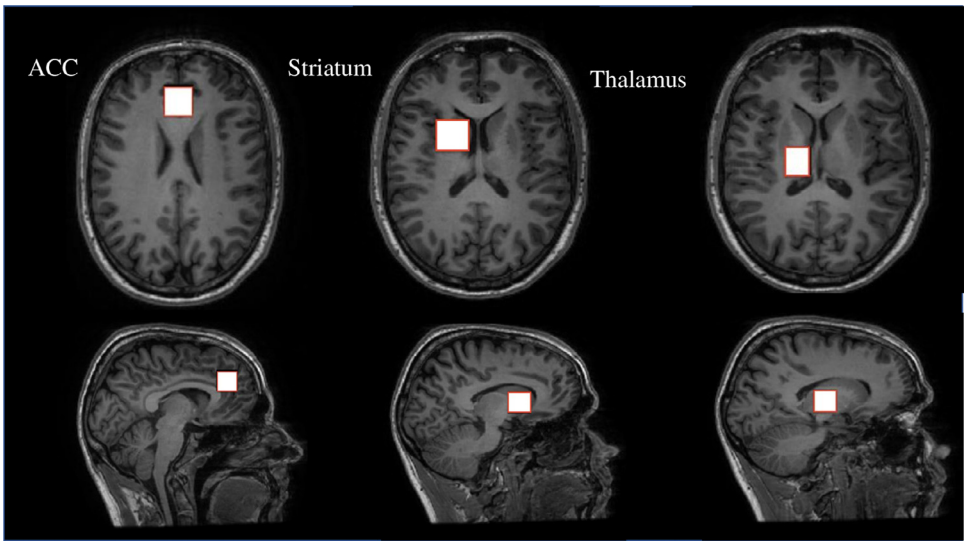

Fig. 1 Voxel in anterior cingulate cortex, left striatum and left thalamus.

2. Experimental procedures

Ethical permission was obtained from the London-West London & GTAC Research Ethics Committee. Following description of the study, informed written consent was given by all participants.

2.1. Sample size

A previous spectroscopy study in a familial high risk group for psychosis found an elevation in thalamic Glx in the high risk group relative to controls with an effect size of Cohen's $d = 0.88$ (Tandon et al., 2013). A power calculation was conducted using the G*Power software version 3.1 (Faul et al., 2009), and showed that a sample size of 22 per group gives 80% power to detect a difference between groups with an effect size of 0.88 using an independent *t*-test with alpha$<$0.05 (two tailed).

2.2. Participants

23 individuals with 22q11.2 deletion were recruited via support groups in Great Britain and Ireland. Inclusion criteria were: age above 18 years old and confirmed diagnosis of 22q11.2 deletion based on medical records. 30 healthy controls were recruited via local media. Inclusion criteria for controls were: no significant personal medical or psychiatric history, no family history of psychotic disorder, no neuropsychiatric disorder and no concurrent use of psychotropic medication. Exclusion criteria for both groups: history of head trauma, significant medical or neurological disorder (unrelated to 22q11.2 deletion), significant illicit drug/ alcohol use, any procedures, operations or medical conditions (e.g. pregnancy) that would compromise MRI safety.

2.3. Clinical assessments

All participants with 22q11.2 deletion were assessed using the Comprehensive Assessment of At Risk Mental States (CAARMS), which measures sub-clinical psychotic-like symptoms (Yung et al., 2005). Subjects also received the short version of the Oxford-Liverpool Inventory of Feelings and Experiences (O-Life) questionnaire (Mason et al., 2005). In addition, they completed Beck's self-report questionnaires for Depression (Beck et al., 1996) and Anxiety (Beck et al., 1988). Intelligence Quotient was measured using an abbreviated version of the Wechsler Adult Intelligence scale (WAIS-III)(Wechsler, 1997), consisting of 4 subtests (Blyler et al., 2000).

2.4. ^{1}H-MRS acquisition

All scans were acquired in a 3 Tesla scanner (General Electric, Chicago, IL, USA). The voxels for MRS measurements were placed on the ACC, left striatum and thalamus. The ACC voxel was defined from the midline sagittal localizer, with the center of the 20 mm $\times$ 20 mm $\times$ 20 mm voxel placed 16 mm above the genu of corpus callosum perpendicular to the AC-PC line (Figs. 1 and 2). A 20 mm x 20 mm x 20 mm voxel was placed on the left striatum to include the maximum amount of striatal gray matter and minimize inclusion of cerebrospinal fluid or insular tissue (Figs. 1 and 2). In addition, the voxel (15 $\times$ 20 $\times$ 20) in the left thalamus was placed at the point in the coronal slices where the thalamus was widest and free from cerebrospinal fluid contamination (Figs. 1 and 2). MRS spectra (Point RESolved Spectroscopy; TE = 30 ms; TR = 3000 ms; 96 averages; bandwidth = 5 kHz, number of data points = 4096) were acquired using the standard GE PROBE (proton brain examination) sequence. Additional unsuppressed water reference spectra (16 averages) were acquired for eddy current correction and water scaling. Shimming was optimized with auto-prescan performed twice before each scan (Egerton et al., 2012, 2014).

2.5. ^{1}H-MRS analysis

Spectra were analysed using LC Model version 6.3-1 L (Provencher, 2016). Voxel GM, WM, and CSF content for each subject were derived by extracting the location of the voxel from the spectra file headers and using an in-house program to calculate the percentage of GM, WM, and CSF using the segmented T1-weighted images. Water-scaled metabolites were corrected for CSF using the formula: metabolite corrected = metabolite concentration $\times$ [proportion WM + (1.21 $\times$ proportion GM) + (1.548 $\times$ proportion CSF)]/ (proportion WM + proportion GM). Poorly fitted metabolite peaks (Cramer-Rao minimum variance bounds $>$20% or Signal to Noise ratio$<$ 8, as reported by LC Model) were excluded from further analysis.

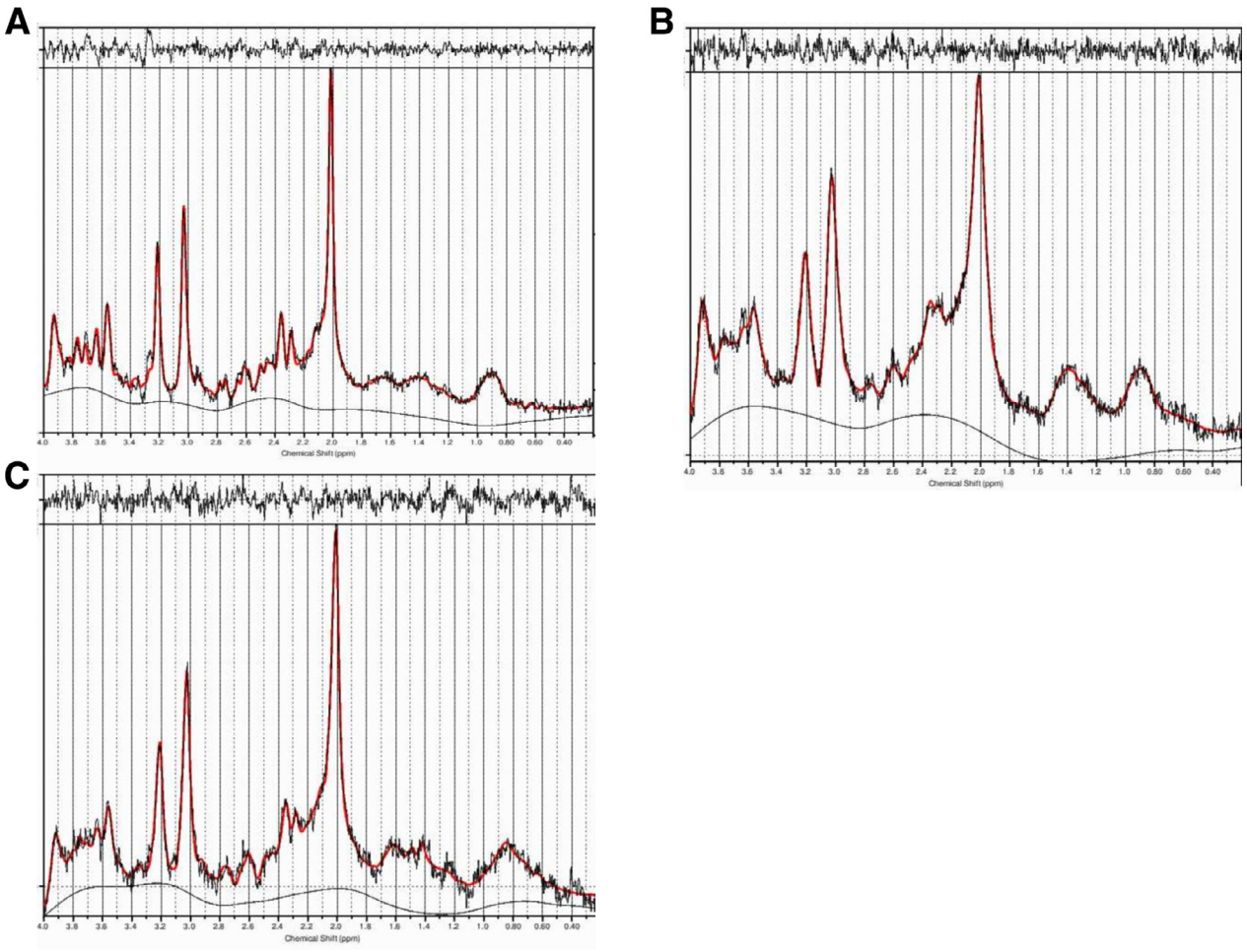

Fig. 2 Sample spectra in A. Anterior cingulate cortex, B. Striatum and C. Thalamus.

2.6. Statistical analysis

Statistical analyses were performed using SPSS, version 24 (IBM SPSS Statistics for Macintosh, Version 24.0), and significance set at $p \leq 0.05$ (two-tailed). Normality of distribution was assessed using the Shapiro-Wilk test. Differences in demographic and clinical variables were assessed using two-tailed independent samples t-tests or Pearson chi square as appropriate. To test our primary hypothesis, independent sample t-tests was used for normally distributed data and Mann-Whitney for not normally distributed data. A secondary analysis was also performed in the sample of 22q11.2 deletion with no history of psychotic disorder and no history of antipsychotic treatment. We also conducted an exploratory sub-analysis in our sample for the individuals below the age of 26, based on previous literature that suggested that more than 40% individuals with 22q11.2 deletion will develop a schizophreniform disorder by the age of 26 years old (Schneider et al., 2014). In order to test our second hypothesis, we calculated Pearson's correlation coefficients (for normally distributed data) or Spearman's correlation coefficients (for non-normally distributed data) between Glx levels and clinical scales.

3. Results

3.1. Demographics

Demographic details for both groups are given in Table 1. There were no significant differences between groups in age, gender, or ethnicity (all p values$>$ 0.05). Two individuals with 22q11.2 deletion were being treated with antipsychotic medication (olanzapine 20 mg/day and aripiprazole 2.5 mg/day), one for schizophrenia and the other for behavioural disturbances. No other participants were receiving any psychotropic medication.

3.2. Spectra quality data

Levels of Glx in the ACC and striatum were normally distributed, but were not normally distributed in the thalamus. Spectra quality data can be found in Supplementary Table 1.

3.3. Glx levels in anterior cingulate cortex, left striatum and thalamus

Results for Glx levels in the ACC, left striatum and thalamus are presented in Table 2. One individual with 22q11.2 deletion was excluded from the ACC analysis due to low signal to noise ratio. In the striatum, four individuals with 22q11.2 deletion were removed due to either low S/N ratio or increased Cramer-Rao variance as described in the Methods. Moreover, metabolites peaks for Glx in the thalamus

Table 1 Demographic details of individuals with 22q11.2 deletion and healthy controls.

	22q11.2 deletion	Healthy controls	*p*-value
N	23	30	
Age	28.61(10.6)	27.63(6.02)	0.69
Gender (Male: Female)	8:15	14:16	0.38
Ethnicity	22 Caucasian, 1 Afrocaribbean	28 Caucasian, 1 African 1 Asian	0.67
Tobacco use (Never: Past: Current)	19:0:4	20:3:7	0.23
CAARMS total score (Mean (SD))	23.36(14.3)	n/a	
CAARMS positive score (Mean (SD))	5.09(4.68)	n/a	
CAARMS negative score (Mean (SD))	2.82(2.67)	n/a	
O-Life questionnaire subscales			
i) Unusual experiences	2.17 (2.1)	0.76 (1.06)	0.006
ii) Cognitive Disorganization	5.83(2.9)	1.83(1.44)	<0.001
iii) Introvertive Anhedonia	4.13 (2.28)	0.93(1.07)	<0.001
iv) Impulsive Non-confirmity	2.09 (1.73)	0.9(0.9)	0.002
Beck's Depression scale score (Mean (SD))	6.87 (7.61)	1.7 (3.8))	0.006
Beck's Anxiety scale score (Mean (SD))	17.26(14.06)	8.73 (7.79)	0.013
FSIQ (Mean (SD))	80.48 (20.66)	131.53(17.56)	<0.001

Table 2 Glx Measures in the anterior cingulate, striatum and thalamus Mean± SD (N) for individuals with 22q11.2 deletion and healthy controls.

	ACC			Striatum			Thalamus		
	22q11.2 deletion	Healthy controls	*p*	22q11.2 deletion	Healthy controls	*p*	22q11.2 deletion	Healthy controls	*p*
Glx	19.83± 3.09 ($N=22$)	21.09 ±3.85 ($N=30$)	0.21	12.11± 3.17 ($N=19$)	11.49 ±2.76 ($N=30$)	0.49	10.25± 3.47 ($N=22$)	10 ±2.87 ($N=29$)	0.8

Table 3 Glx Measures in the anterior cingulate, striatum and thalamus, Mean± SD (N) for individuals with 22q11.2 deletion without psychosis or antipsychotic treatment and healthy controls.

	ACC			Striatum			Thalamus		
	22q11.2 deletion	Healthy controls	*p*	22q11.2 deletion	Healthy controls	*p*	22q11.2 deletion	Healthy controls	*p*
Glx	19.97± 3 ($N=20$)	21.09 ±3.85 ($N=30$)	0.28	11.92± 3.3 ($N=17$)	11.49 ±2.76 ($N=30$)	0.79	10.42± 3.5 ($N=20$)	10.06 ±2.87 ($N=29$)	0.9

were excluded from further analysis for one individual with 22q11.2 deletion due to > 20% of Cramer Rao.

There were no significant between group differences in Glx for the ACC, striatum or thalamus ($t(50)=-1.26$, $p=0.21$; $U=251$, $z=-0.7$, $p=0.49$, $U=316$, $z=-0.26$, $p=0.8$, respectively) (Table 2, Fig. 3). In addition, a secondary analysis was performed, excluding the two subjects taking antipsychotic treatment so as to restrict the group to antipsychotic naïve individuals. This resulted in the inclusion of 20 people with 22q11.2 deletion and showed no significant differences between groups for Glx levels in any of the brain regions (Table 3). Similarly, the sub-analysis in individuals below the age of 26 years old ($N=11$ for individuals with 22q11.2 deletion and $N=14$ for healthy controls) did not alter our results (Supplementary Table 2).

3.4. Relationship between glutamatergic function and symptoms

There was no association between Glx in the ACC, striatum or thalamus and at-risk mental state symptom scores; (CAARMS total score ($r=-0.05$, $p=0.81$; $r=0.13$, $p=0.62$, $r=0.12$, $p=0.62$, respectively); CAARMS positive score ($r_s=0.2$, $p=0.37$; $r_s=0.12$, $p=0.64$, $r_s=0.01$, $p=0.96$, respectively); CAARMS negative score ($r=0.37$, $p=0.094$; $r=0.13$, $p=0.62$, $r_s=0.11$, $p=0.63$, respectively). Moreover, we found no relationship between Glx in the ACC, striatum or thalamus with FSIQ ($r_s=0.14$, $p=0.54$; $r_s=0.03$, $p=0.9$; $r_s=0.2$, $p=0.38$, respectively).

In exploratory analyses, we also examined if there was any relationship between Glx in the ACC, striatum or tha-

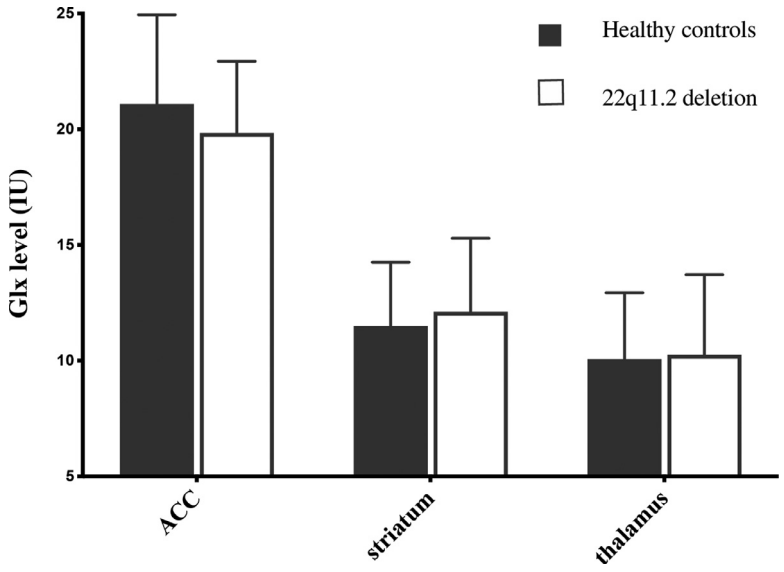

Fig. 3 Gx levels in the anterior cingulate cortex, striatum and thalamus, error bars indicate SD.

lamus with the other clinical scales. Similarly, results remained non-significant in all brain regions (for more information, please see supplementary material).

We also investigated if there is any correlation between Glx levels in the ACC, striatum or thalamus with clinical measures in the healthy control group. Likewise, no significant association was detected (for more information, please see supplementary material).

4. Discussion

Our main findings are that there is no difference in the levels of Glx in the ACC, striatum and thalamus between controls and people at high genetic risk of psychosis secondary to carrying the 22q11.2 deletion. Moreover, there was no association between Glx levels in the ACC, striatum and thalamus with any clinical measures.

There has been only one previous spectroscopy study in individuals with 22q11.2 deletion (da Silva Alves et al., 2011), and this included 11 individuals with 22q11.2 deletion without schizophrenia, 7 individuals with 22q11.2 deletion with schizophrenia and 23 healthy controls. Results showed no difference in glutamate or Glx levels in the dorsolateral prefrontal cortex (DLPFC) between the three groups. In contrast, Glx levels in hippocampus were increased in individuals with 22q11.2 deletion and schizophrenia compared to the individuals without a schizophrenia diagnosis, and to the group of healthy controls. Furthermore, no difference in Glx levels was reported between people with 22q11.2 deletion without schizophrenia and healthy controls. Our study extends these findings by showing in a larger sample that there are no MRS measurable glutamatergic alterations in individuals with 22q11.2 deletion without psychosis.

We found no significant associations between Glx levels and psychosis risk symptom severity, as measured with CAARMS or any of the other rating scales. Our results are in agreement with previous studies in people at familial high risk for psychosis (Tibbo et al., 2004; Yoo et al., 2009), but contrast with findings in CHR (de la Fuente-Sandoval et al., 2011, 2015; Egerton et al., 2014; Stone et al., 2009). In our sample, mean CAARMS scores were relatively low compared to studies including CHR groups (Bloomfield et al., 2016; Howes et al., 2011). Similarly, no correlation was observed between Glx and FSIQ in any brain region, in either group. Evers and colleagues previously reported an inverse correlation between FSIQ and plasma glutamate in 22q11.2 deletion, although two different methods were used to calculate FSIQ in the study depending on the intellectual level (Evers et al., 2015). This inconsistency may be attributed to the fact that levels in the periphery may not directly correspond to levels measured in the brain.

4.1. Strengths and limitations

This is the first spectroscopy study examining glutamatergic function in the ACC, striatum and thalamus in individuals with 22q11.2 deletion. In our secondary analysis, we included only antipsychotic naïve individuals who were in the peak age range for developing psychosis. Our study was cross-sectional and therefore we cannot exclude the possibility that glutamatergic alterations may develop later. Follow-up of our sample is thus required to determine if glutamate related metabolite changes occur with the development of psychosis. In addition, although no abnormalities in glutamatergic function were detected in ACC, striatum or thalamus, we cannot rule out the possibility that these may exist in other brain regions.

Moreover, the possibility of a type II error cannot be excluded. Previous spectroscopy studies in groups of first episode psychosis and high risk for psychosis, including individuals at high familial risk, have shown an in-

crease of Glx levels with effect sizes ranging from 0.66 to 0.88(Allen et al., 2015; de la Fuente-Sandoval et al., 2011; Tandon et al., 2013; Tibbo et al., 2004). The latter group has about 10%-15% risk for developing schizophrenia (Rasic et al., 2013), which is significantly lower compared to the estimated 30% in 22q11.2 deletion. As described in the methods section, a power calculation indicates that our sample size has >80% power to detect an elevation in Glx of Cohen's d effect size of 0.88 or greater. Therefore, we cannot rule out the possibility of smaller elevations, although our data do not show any indication of a trend to support this hypothesis.

A limitation of our study is that we were not able to reliably quantify glutamine (Gln) concentrations. At magnetic fields of 3Tesla or below and with the spectroscopy techniques used until recently, separation of Glu-and Gln-is difficult due to overlapping resonances (Hancu, 2009). Hence, it is possible that there may be a degree of contamination in the Glu-concentration by Gln (Egerton et al., 2012). In addition, as previously discussed, MRS does not allow the distinction between extracellular and intracellular glutamate (Rothman et al., 2011). Glutamate plays an important role in a number of brain metabolic processes, including protein synthesis and mitochondrial energy metabolism (Kovacevic and McGivan, 1983). Hence, it is present in numerous cell types and also in intracellular and extracellular space. The MRS signal measures the total amount of glutamate in a specific brain region but does not distinguish between glutamate involved in different functions or cellular compartments (Wijtenburg et al., 2015). Thus, whilst we show no difference in Glx levels, it remains possible that specific aspects of glutamate neurotransmission are altered in 22q11.2 carriers, but this is masked in the total signal or by compensatory changes.

4.2. Implications for understanding the neurobiology of schizophrenia

We did not detect any difference in Glx levels in ACC, striatum or thalamus in the individuals with 22q11.2 deletion. Taken together with the evidence of the previous spectroscopy study on 22q11.2 deletion, this suggests that glutamatergic abnormalities may be less marked in individuals with an established genetic risk for psychosis, compared to those at clinical high risk for the disorder. Thus, this could indicate that glutamatergic alterations seen in schizophrenia arise with the development of symptoms and may be linked to disease stage, and clinical outcome (Bustillo et al., 2014; de la Fuente-Sandoval et al., 2013; Egerton et al., 2017).

5. Conclusions

Current findings from spectroscopy studies in 22q11.2 deletion do not support the hypothesis that glutamatergic abnormalities exist within this group. Future large-scale, longitudinal studies, using higher field strength MRI scanners or Positron Emission Tomography (PET) studies utilizing glutamatergic radioligands, are needed to disentangle the role of glutamatergic function in 22q11.2 deletion.

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Contributors

OH and MR designed the study and wrote the protocol. MR collected the data and MG, ED, SJ contributed to it. MR conducted the analyses and PH contributed to it. MR wrote the first draft of the manuscript. All authors contributed to and approved the final manuscript.

Declaration of Competing Interest

MR, PH, MG, RM, SJ and ED declare that there are no conflicts of interest in relation to the subject of this study. Oliver Howes has received investigator-initiated research funding from and/or participated in advisory/ speaker meetings organised by Angellini, Astra-Zeneca, Autifony, Biogen, BMS, Eli Lilly, Heptares, Jansenn, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, Rand and Roche. Neither Dr. Howes or his family have been employed by or have holdings/ a financial stake in any biomedical company.

CRediT authorship contribution statement

Maria Rogdaki: Writing - original draft. **Pamela Hathway:** Writing - original draft. **Maria Gudbrandsen:** Writing - original draft. **Robert A. McCutcheon:** Writing - original draft. **Sameer Jauhar:** Writing - original draft. **Eileen Daly:** Writing - original draft. **Oliver Howes:** Writing - original draft.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.09.005.

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