Dopamine and glutamate in individuals at risk for psychosis: a meta-analysis of *in vivo* imaging findings and their variability compared to controls

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Dopaminergic and glutamatergic dysfunction is believed to play a central role in the pathophysiology of schizophrenia. However, it is unclear if abnormalities predate the onset of schizophrenia in individuals at high clinical or genetic risk for the disorder. We systematically reviewed and meta-analyzed studies that have used neuroimaging to investigate dopamine and glutamate function in individuals at increased clinical or genetic risk for psychosis. EMBASE, PsychINFO and MEDLINE were searched form January 1, 1960 to November 26, 2020. Inclusion criteria were molecular imaging measures of striatal presynaptic dopaminergic function, striatal dopamine receptor availability, or glutamate function. Separate meta-analyses were conducted for genetic high-risk and clinical high-risk individuals. We calculated standardized mean differences between high-risk individuals and controls, and investigated whether the variability of these measures differed between the two groups. Forty-eight eligible studies were identified, including 1,288 high-risk individuals and 1,187 controls. Genetic high-risk individuals showed evidence of increased thalamic glutamate + glutamine (Glx) concentrations (Hedges' g=0.36, p=0.003). There were no significant differences between high-risk individuals and controls in striatal presynaptic dopaminergic function, striatal D2/D3 receptor availability, prefrontal cortex glutamate or Glx, hippocampal glutamate or Glx, or basal ganglia Glx. In the meta-analysis of variability, genetic high-risk individuals showed reduced variability of striatal D2/D3 receptor availability compared to controls (log coefficient of variation ratio, CVR= –0.24, p=0.03). Meta-regressions of publication year against effect size demonstrated that the magnitude of differences between clinical high-risk individuals and controls in presynaptic dopaminergic function has decreased over time (estimate=–0.06, 95% CI: –0.11 to –0.007, p=0.025). Other than thalamic glutamate concentrations, no neurochemical measures were significantly different between individuals at risk for psychosis and controls. There was also no evidence of increased variability of dopamine or glutamate measures in high-risk individuals compared to controls. Significant heterogeneity, however, exists between studies, which does not allow to rule out the existence of clinically meaningful differences.

Key words: Schizophrenia, dopaminergic dysfunction, glutamatergic dysfunction, clinical high risk, genetic high risk, thalamic glutamate, presynaptic dopaminergic function, dopamine receptor availability

Disruption of dopaminergic and glutamatergic neurotransmission has been proposed to be central to the pathophysiology of schizophrenia[1-4]. Single photon computed emission tomography (SPECT) and positron emission tomography (PET) allow the dopamine system to be studied *in vivo*, while *in vivo* quantification of glutamate levels is possible using proton magnetic resonance spectroscopy (^{1}H-MRS).

Meta-analyses of available studies have found consistent evidence of higher striatal dopamine synthesis and release capacity in schizophrenia, and shown that this is greatest in the associative region of the striatum[5,6]. In contrast, meta-analyses of studies investigating dopamine D2/D3 receptor availability have not shown significant patient-control differences in schizophrenia, although reporting increased variability in receptor availability[6-9].

Meta-analyses of studies examining glutamate function have shown that, in individuals with psychosis, glutamate levels are higher in the basal ganglia, the glutamate metabolite glutamine is higher in the thalamus, while glutamate in combination with glutamine (Glx) is higher in the hippocampus[1]. In the frontal cortex, a recent meta-analysis of 7-Tesla studies reported lower glutamate in patients[10].

These findings indicate that dopamine and glutamate dysfunction occurs in schizophrenia, but raise the question of whether it predates the onset of the disorder. It is possible to investigate neurochemical changes prior to the onset of schizophrenia by studying people at increased risk for developing the disorder.

The presence of sub-clinical symptoms prior to the development of psychosis has long been recognized[11]. People with schizotypal disorder experience sub-clinical psychotic symptoms, and are at increased risk of developing psychotic disorders, predominantly schizophrenia, with a risk of 25-48% over long-term follow-up[12-14]. The introduction of structured clinical assessments has also allowed the identification of individuals at clinical high risk (CHR) for psychosis, in whom the risk of transition to psychosis is around 20-30% over two years[15]. To meet criteria for CHR, a person is required to show one or more of the following at or above threshold levels: schizotypal disorder plus recent onset functional impairment, and/or brief intermittent psychotic symptoms, and/or attenuated psychotic symptoms[16].

In addition to studying individuals at increased clinical risk, research has also been undertaken to quantify neurochemical functioning in individuals at genetic high risk (GHR) for schizophrenia. These studies have either investigated non-psychotic relatives of individuals with schizophrenia, or individuals with copy number variants, such as the copy number deletion of 1.5-5 megabases at 22q11.2, which is associated with a ~45% lifetime risk of developing psychosis and ~35% lifetime risk of developing schizophrenia[17,18].

There is some evidence that neurochemical dysfunction may primarily exist in a subgroup of high-risk individuals who subsequently develop psychosis[19,20]. If neurochemical alterations occur only in a subgroup of high-risk individuals, this would be expected to lead to increased

variability of the parameter in question in the high-risk group[21]. Novel meta-analytic techniques now allow for the quantification of variability across studies[22-24]. It is therefore possible to test meta-analytically the hypothesis that greater variability of dopamine and glutamate measures exists in high-risk individuals compared to controls.

A number of ^{1}H-MRS, PET and SPECT studies have investigated dopamine and glutamate functioning in CHR and GHR groups[25-28], but to our knowledge no meta-analyses of the dopamine findings has been undertaken, and an earlier meta-analysis of the glutamate findings[29] is now outdated, since six new studies have been published after it was conducted[30-35], increasing the sample size by 574 subjects. Moreover, variability has never been investigated for either dopamine or glutamate studies.

In the present paper, we meta-analyze neuroimaging studies of the dopamine and glutamate systems in individuals at high clinical or genetic risk for psychosis to provide the best estimate of the magnitude and variability of group differences across samples and settings.

METHODS

Search strategy and study selection

EMBASE, PsychINFO and MEDLINE were searched from January 1, 1960 to November 26, 2020. Titles and abstracts were searched for the words (“schizophrenia” OR “psychosis” OR “schizophreniform” OR “prodrom*” OR "at risk mental state" OR "high risk" OR “22q” OR 16p OR “vcfs” OR “velocardiofacial”) AND ("positron emission tomography" OR "PET" OR "single photon emission tomography" OR “SPET” OR "single photon emission computed tomography" OR “SPECT” OR "MRS" OR “spectroscopy”) AND (“dopamine” OR “glutamate”).

We included studies of: a) subjects meeting established research criteria for having an at risk mental state for psychosis determined using a structured assessment instrument (the Comprehensive Assessment of At-Risk Mental States[36] or the Structured Interview for Prodromal Symptoms[37]); b) subjects meeting DSM or ICD criteria for a diagnosis of schizotypal personality disorder/schizotypal disorder; and c) non-psychotic people at increased genetic risk for schizophrenia (for example, relatives of individuals with schizophrenia, or non-psychotic individuals with a diagnosis of 22q11.2 deletion syndrome or 16p11.2 duplication syndrome). These studies had to report one or more imaging measures of striatal presynaptic dopaminergic function, striatal D2/D3 receptor availability, glutamate or glutamate + glutamine (Glx) concentrations, for patient and control groups. As in previous meta-analyses[5,6], studies of striatal presynaptic dopamine function included those of

dopamine synthesis capacity, dopamine release capacity, and synaptic dopamine levels. Furthermore, studies had to provide data enabling the estimation of standardized mean differences between patient and control groups for the relevant parameter.

We excluded data in individuals with comorbid substance dependence, as this may have significant effects on the dopamine system[38-40].

Data extraction

The primary outcome of interest was the imaging parameter reported for patient and control groups. In addition, first author, year of study, number of participants, participant age, participant gender, antipsychotic treatment, transitions to psychosis observed over clinical follow-up, and symptom scores were extracted.

Where dopamine measures for the whole striatum were not provided, but data for the caudate and putamen were reported, whole striatum values were calculated by weighting these values by their volumes as reported in the Oxford-GSK-Imanova Structural-Anatomical Striatal Atlas (43% and 57% respectively). If data for ventral striatum were reported, the following weightings were used to derive a summary outcome for the whole striatum: 36% for caudate, 48% for putamen, and 16% for ventral striatum[41]. If only functional subdivisions were reported, the following weightings – based on templates used in previous imaging studies[25,42] – were used to derive a summary outcome for the whole striatum: 12.1% for limbic striatum, 61.9% for associative striatum, and 26.0% for sensorimotor striatum.

Data analysis

For the meta-analysis of mean differences, standard effect sizes (Hedges' g) for individual studies were estimated.

The relative variability of imaging measures in high-risk individuals compared to controls can be quantified using the variability ratio (VR), where ln is natural logarithm; $\hat{\sigma}_h$ and $\hat{\sigma}_c$ are the unbiased estimates of the population standard deviation for the high-risk and control groups; S_h and S_c are the reported standard deviations, and n_h and n_c are the sample sizes.

$$\mathrm{VR} = \ln\left(\frac{\hat{\sigma}_h}{\hat{\sigma}_c}\right) = \ln\left(\frac{S_h}{S_c}\right) + \frac{1}{2(n_h - 1)} - \frac{1}{2(n_c - 1)}$$

In biological systems, however, variance often scales with mean[22,23], and we therefore used the log coefficient of variation ratio (CVR) as our primary outcome measure in this analysis, where $\bar{x}_h$ and $\bar{x}_c$ are the mean symptom scores of high risk and control groups.

$$\mathrm{CVR} = \ln\left(\frac{\hat{\sigma}_h/\bar{x}_h}{\hat{\sigma}_c/\bar{x}_c}\right) = \ln\left(\frac{S_h/\bar{x}_h}{S_c/\bar{x}_c}\right) + \frac{1}{2(n_h-1)} - \frac{1}{2(n_c-1)}$$

All statistical analyses were carried out using the 'metafor' package (version 2.0.0) in the statistical programming language R (version 3.3.1). Separate meta-analyses were conducted for GHR and CHR individuals. For dopamine studies, a distinction was made between studies of presynaptic dopaminergic function and those of D2/D3 receptor availability. Glutamate studies were analyzed separately both on the basis of the region studied and on whether they assessed glutamate or Glx. Meta-analysis was only performed if at least three eligible studies were available. Egger's test, funnel plots and trim and fill analyses were conducted to test for publication bias, and the I^2 statistic was used to quantify study inconsistency.

In both the meta-analysis of standardized mean differences and that of CVR, individual study effect sizes were entered into a random effects meta-analytic model using restricted maximum likelihood estimation.

The time period of risk is longer in people with schizotypal disorder compared to individuals meeting criteria for an at-risk mental state. Sensitivity analyses were therefore conducted to determine the effect of excluding the studies of schizotypal disorder on the findings.

Meta-regressions were undertaken to investigate potential associations between study effect sizes and age, gender composition and publication year. These analyses were performed in all instances where there were at least five eligible studies.

A significance level of $p<0.05$ (two-tailed) was used for all analyses.

RESULTS

A total of 5,455 papers were identified. Forty-eight of these met inclusion criteria, reporting data on 1,288 high-risk individuals and 1,187 controls (Figure 1). The average age of study participants was 26.5 years, and 52.6% of participants were male.

Striatal presynaptic dopaminergic function in clinical high-risk subjects

Eight studies of CHR individuals met inclusion criteria[18,42-48] (see Table 1). The studies included a total of 188 CHR individuals and 151 controls. The two groups did not differ significantly in terms of striatal presynaptic dopaminergic function (Hedges' g=0.28, 95% CI: –0.03 to 0.59, p=0.07) (see Figure 2). The I^2 value was 46%, indicating moderate between-study inconsistency. Neither Egger's test (p=0.75) nor trim and fill analysis suggested publication bias.

A sensitivity analysis excluding the two studies of schizotypal disorder was conducted, and provided similar results (Hedges' g=0.25, 95% CI: –0.10 to 0.60, p=0.17). When the six studies reporting functional subdivisions were analyzed on a by-subdivision basis, there was no evidence for differences in striatal presynaptic dopaminergic function for any subdivision (associative: g=0.20, p=0.20; sensorimotor: g=0.20, p=0.12; limbic: g=0.21, p=0.26).

The meta-analysis of variability did not show differences in variability for CHR individuals compared to controls (CVR=0.13, 95% CI: –0.01 to 0.27, p=0.06) (see Figure 3).

Striatal presynaptic dopaminergic function in genetic high-risk subjects

Six studies reported findings in individuals at increased genetic risk for schizophrenia, four of which examined relatives of individuals with schizophrenia[27,28,49,50], and two reported findings in individuals with 22q11 deletion syndrome[51,52] (see Table 1). These studies reported data on 81 GHR individuals and 105 controls. There was no significant difference in striatal presynaptic dopaminergic function between the two groups (Hedges' g=0.24, 95% CI: –0.40 to 0.88, p=0.46) (see Figure 2). The I^2 statistic was 77%, indicating substantial between-study inconsistency. Egger's test was significant (p=0.02), although a trim and fill analysis did not suggest any potentially missing studies.

The meta-analysis of variability did not show differences in variability for GHR individuals compared to controls (CVR= –0.04, 95% CI: –0.25 to 0.17, p=0.72) (see Figure 3).

Striatal D2/D3 receptor availability in clinical high-risk subjects

Five studies[43,46-48,53] examined striatal D2/D3 receptor availability in 83 CHR individuals and 79 controls (see Table 1). There were no significant differences between the two groups (Hedges' g=–0.08, 95% CI: –0.48 to 0.33, p=0.70) (see Figure 2). The I^2 value was 39%, indicating moderate between-study inconsistency. Neither Egger's test (p=0.9) nor trim and fill analysis suggested publication bias.

The meta-analysis of variability did not show differences in variability for CHR individuals compared to controls (CVR=0.11, 95% CI: –0.17 to 0.39, p=0.43) (see Figure 3).

Striatal D2/D3 receptor availability in genetic high-risk subjects

Five studies[28,51,53-55] examined striatal D2/D3 receptor availability in 57 GHR individuals and 61 controls. There was no significant difference between the two groups (Hedges' g=–0.03, 95% CI: –0.39 to 0.34, p=0.88) (see Figure 2). The I^2 value was 0%, indicating low

between-study inconsistency. Neither Egger's test (p=0.9) nor trim and fill analysis suggested publication bias.

The meta-analysis of variability showed significantly reduced variability for GHR individuals compared to controls (CVR=–0.24, 95% CI: –0.46 to –0.02, p=0.03) (see Figure 3).

Glutamate function in clinical high-risk subjects

Three studies[35,56,57] measured glutamate (215 CHR individuals, 133 controls), and ten studies[33,35,56-63] measured Glx (375 CHR individuals, 306 controls) in the prefrontal cortex (see Table 2). Neither set of studies found any significant differences between CHR individuals and controls (glutamate: g=0.01, 95% CI: –0.21 to 0.22, p=0.96; Glx: g=0.01, 95% CI: –0.15 to 0.16, p=0.92) (see Figure 2). Both glutamate and Glx studies showed low between-study inconsistency (I^2=0%). Neither set of studies showed evidence of publication bias as examined using Egger's test (glutamate: p=0.63; Glx: p=0.93) and trim and fill analysis.

There were no significant variability differences in either glutamate or Glx between CHR individuals and controls (glutamate: CVR=0.18, 95% CI: –0.12 to –0.48, p=0.24; Glx: CVR=0.08, 95% CI: –0.05 to 0.20, p=0.23) (see Figure 3).

Five studies[30,64-67] measured glutamate (177 CHR individuals, 141 controls), and five studies[30,34,64,67,68] measured Glx (240 CHR individuals, 126 controls) in the hippocampus (see Table 2). Neither set of studies found any significant differences between CHR individuals and controls (glutamate: g=–0.26, 95% CI: –0.56 to 0.04, p=0.09; Glx: g=0.13, 95% CI: –0.43 to 0.69, p=0.66) (see Figure 2). Between-study inconsistency was lower in the glutamate (I^2=36%) compared to the Glx studies (I^2=83%). Neither set of studies showed evidence of publication bias as examined using Egger's test (glutamate: p=0.10; Glx: p=0.78) or trim and fill analyses.

Neither set of studies showed significant variability differences between CHR individuals and controls (glutamate: CVR= –0.05, 95% CI: –0.29 to 0.18, p=0.66; Glx: CVR=0.03, 95% CI: –0.11 to 0.17, p=0.64) (see Figure 3).

Three studies[35,56,58] measured Glx (200 CHR individuals, 130 controls) in the thalamus. They found overall no significant differences between the two groups (Hedges' g = –0.17, 95% CI: –0.40 to 0.05, p=0.13) (see Figure 2). Between-study inconsistency was low (I^2=0%) and there was no evidence of publication bias (Egger's test: p=0.85).

There was no evidence of variability differences between CHR individuals and controls for the primary outcome measure (CVR=–0.21, 95% CI: –0.45 to 0.04, p=0.10) (see Figure 3). However, the VR was reduced in CHR individuals compared to controls (VR=–0.23, 95% CI: –0.45 to –0.01, p=0.04).

Glutamate function in genetic high-risk subjects

Five studies[32,70-73] measured glutamate (96 GHR individuals, 105 controls), and nine studies[31,32,70,71,74-78,] measured Glx (210 GHR individuals, 259 controls) in the prefrontal cortex (see Table 2). Neither set of studies found any significant differences between GHR individuals and controls (glutamate: g=0.15, 95% CI: –0.20 to 0.50, p=0.39; Glx: g=0.14, 95% CI: –0.10 to 0.37, p=0.26) (see Figure 2). Glutamate and Glx studies showed similar levels of between-study inconsistency (glutamate: I^2=43%; Glx: I^2=34%). Neither set of studies showed evidence of publication bias as examined using Egger's test (glutamate: p=0.40; Glx: p=0.71) and trim and fill analysis.

There were no significant variability differences in either glutamate or Glx between GHR individuals and controls (glutamate: CVR=0.04, 95% CI: –0.27 to –0.35, p=0.81; Glx: CVR= 0.05, 95% CI: –0.13 to 0.23, p=0.59) (see Figure 3).

Four studies[31,32,75,78] measured Glx in the thalamus in 113 GHR individuals and 163 controls (see Table 2). There were insufficient studies of glutamate alone to meta-analyze. Glx concentrations were significantly raised in GHR individuals compared to controls (Hedges' g=0.36, 95% CI: 0.12 to 0.61, p=0.003) (see Figure 3). The I^2 value was 0%, suggesting low between study inconsistency. Both Egger's test (p=0.9) and trim and fill analysis did not indicate publication bias.

There was no evidence of variability differences (CVR=0.10, 95% CI: –0.08 to 0.27, p=0.30) (see Figure 3).

Five studies[31,74,78-80] measured Glx in the basal ganglia in 138 GHR individuals and 145 controls (see Table 2). There were insufficient studies of glutamate alone to meta-analyze. There was no significant difference in Glx concentrations between GHR individuals and controls (Hedges' g=0.07, 95% CI: –0.30 to 0.44, p=0.71) (see Figure 2). The I^2 value was 55%, indicating moderate between-study inconsistency. Neither Egger's test (p=0.93), nor trim and fill analysis suggested the possibility of publication bias.

There was no evidence of variability differences (CVR=–0.11, 95% CI: –0.26 to 0.05, p=0.17) (see Figure 3).

Meta-regressions

The magnitude of CHR-control differences in striatal presynaptic dopaminergic function and D2/D3 receptor availability was greater in studies published earlier (presynaptic dopaminergic function: estimate=–0.06, 95% CI: –0.11 to –0.007, p=0.025; D2/D3 receptor

availability: estimate=–0.06, 95% CI: –0.12 to –0.007, p=0.028) (Figure 4). Publication year did not show a significant association with any measure of glutamate function.

The magnitude of GHR-control differences in hippocampal glutamate levels were greater in those studies containing a greater proportion of male patients (estimate=0.07, 95% CI: 0.006-0.13, p=0.030) (Figure 4). Gender was not associated with any other measure. Participant age did not show any significant relationship for any measure.

DISCUSSION

Our first main finding is that thalamic Glx is higher in people at genetic high risk for psychosis relative to controls, with a small to moderate effect size (g=0.36), while there are no marked differences in glutamate or dopamine measures in other brain regions so far examined. Our second main finding is that there are unlikely to be marked differences in dopamine or glutamate measures in people at clinical high risk for psychosis relative to controls.

Although we did not find significant differences in striatal presynaptic dopamine measures between people at clinical or genetic high risk for psychosis and controls, the confidence intervals include moderate to large effects and, in the case of people at clinical high risk for psychosis, these effects approach significance, indicating that it is premature to rule out the possibility of significant group differences.

We found evidence for lower variability of striatal D2/D3 receptor availability in people at genetic risk for schizophrenia relative to controls. In contrast, there was no evidence of significantly greater variability in high-risk individuals compared to controls for any measure.

Dopamine function

Initial studies of striatal presynaptic dopaminergic function in CHR individuals provided evidence of striatal dopaminergic hyperactivity[25,43,44]. The lack of a significant difference between CHR subjects and controls in the current meta-analysis is therefore potentially surprising. It should, however, be considered in the light of four pieces of evidence: the wide confidence interval around the estimated average effect (g=0.28, 95% CI: –0.03 to 0.59); the negative correlation between effect size and publication year; the finding that transition to psychosis rates have diminished over time[15]; and the fact that striatal dopaminergic hyperactivity may be specific to individuals who go on to develop psychosis, rather than all CHR subjects[18].

Rates of transition to a psychotic disorder in clinical high-risk subjects have decreased from 30-40% to 15-20% in more recent studies[15]. This is reflected in the imaging studies included in our analyses, where studies in the last two years[42,47] report transition rates of 20% and 14% respectively, whereas a 2011 study reported a rate of 38%[18]. Thus, the lack of observed differences between CHR individuals and controls may result from more recent study cohorts containing a lower proportion of individuals who transition to psychosis, and therefore a lower proportion of individuals with striatal dopaminergic hyperactivity.

No significant dopaminergic abnormalities were found in individuals at increased genetic risk for schizophrenia. There was, however, again a wide confidence interval around the estimated effect for presynaptic dopaminergic function (g=0.24, 95% CI: –0.40 to 0.88). An important factor to consider is that many of these studies were conducted in relatives of individuals with schizophrenia, who may not carry risk genes for the disorder, and the studies did not actually confirm that subjects were carrying risk genes. Moreover, many of the subjects included were older than the age of peak risk for onset of schizophrenia (the mean age of subjects scanned was 33.7 years). Thus, it is quite possible that the individuals studied were not genetically enriched for schizophrenia risk.

In the case of the 22q deletion studies, the subjects were tested to directly confirm that they were at increased genetic risk. One of these studies demonstrated a large increase in dopamine synthesis capacity in 22q11.2 deletion carriers relative to controls[52]. Future research could benefit from exploring the relationship between measures of neurochemical function and other more direct measures of genetic risk such as polygenic risk scores.

We found no mean differences in striatal D2/D3 receptor availability in either risk group compared to controls. This is consistent with findings in schizophrenia[6]. PET studies of D2/D3 receptors are complicated by the fact that endogenous dopamine competes with the radioligand, which could mask a concurrent rise in receptor density[6,8], although findings to date do not indicate differences in synaptic dopamine levels[65]. We found significantly reduced variability in GHR individuals for measures of striatal D2/D3 receptor availability. This suggests that GHR individuals show greater neurobiological homogeneity, potentially due to increased within-group genetic similarity.

Glutamate function

A previous meta-analysis found that prefrontal Glx was significantly greater in high-risk individuals compared to healthy controls[1]. In our meta-analysis, we were able to include seven further studies for this region, and with these additional studies no difference between groups was found. This finding has the tightest confidence interval of all our results (g=0.01, 95% CI:

–0.15 to 0.16), suggesting that, if any case-control differences do exist, they will at most be of a small magnitude.

Our findings for prefrontal glutamate, hippocampal glutamate and Glx, and basal ganglia Glx include more subjects than the previous meta-analysis, but are in keeping with its findings, in that no group differences were observed in these regions. However, confidence intervals tended to be wider for these regions and it is therefore not possible to conclusively rule out significant between-group differences.

The finding of increased thalamic Glx in GHR individuals adds to the evidence of raised thalamic glutamine in schizophrenia, although we did not detect significant Glx alterations in CHR subjects and there is no evidence of Glx differences in schizophrenia[1].

Methodological considerations

Moderate between-study inconsistency was seen in most of the analyses undertaken. In addition to methodological factors such as differences in scanners, ligands used and voxel positioning, differences in the clinical characteristics of patients could contribute to between-study heterogeneity. Once again, increased dopaminergic activity in clinical high-risk groups may be restricted to those that experience clinical deterioration[81-83]. Similarly, for glutamate, elevations may only occur in high-risk individuals with poor outcomes, which may explain the near-significant effect size detected for hippocampal glutamate. This is supported by reports that elevated hippocampal glutamate levels are specific to individuals who go on to transition[30], and that medial temporal glutamate levels are positively associated with symptom severity in schizophrenia[84].

The use of antipsychotics is unlikely to have had a significant impact on our findings, given that the vast majority of studies reported on antipsychotic-naïve cohorts. However, the use of other psychotropic drugs was not reported in many studies, and could contribute to inconsistencies. A recommendation for future studies is that all psychotropic drug use is reported to facilitate comparisons.

We combined studies of synthesis capacity, release capacity and synaptic dopamine levels, as in previous meta-analyses[5,6]. There is, however, evidence that these paradigms capture separate, although related, aspects of dopaminergic function[85-87].

Future directions

Our review has identified a number of sources of phenotypic heterogeneity that have not been fully addressed in currently available studies. In the case of GHR individuals, characterization of the genetic risk is needed to determine if subjects are indeed at risk. This

in turn should allow for more precise estimates of any potential neurochemical abnormalities. In CHR subjects, key factors are the transition risk, age and specific symptoms[88]. In both groups, larger samples and clinical follow-up of subjects to determine transition are also key.

We focused on striatal presynaptic dopaminergic function and D2/D3 receptor availability, as these variables were measured in a sufficient number of studies to allow a meta-analysis. Recent studies have, however, looked at cortical and nigrostriatal dopaminergic function[46,89]. It would be useful for future studies to combine measures of cortical and nigrostriatal dopaminergic function to determine the regional specificity of findings. It would also be of interest to see if effect sizes are greater in studies where the patient population show greater severity of symptoms, which is currently precluded by the fact that many differing scales are used to assess symptoms.

CONCLUSIONS

Increased thalamic Glx concentrations are found in individuals at increased genetic risk for psychosis. There are no significant differences between high-risk individuals and controls in striatal presynaptic dopaminergic function, striatal D2/D3 receptor availability, prefrontal cortex glutamate or Glx, hippocampal glutamate or Glx, or basal ganglia Glx. There is also no evidence of increased variability of dopamine or glutamate measures in high-risk individuals compared to controls. Significant heterogeneity, however, exists between studies, which does not allow to rule out an increase in striatal dopamine synthesis and release capacity in subjects at increased clinical risk.

ACKNOWLEDGEMENTS

R.A. McCutcheon' s work is funded by a Wellcome Trust grant (no. 200102/Z/15/Z) and UK National Institute for Health Research (NIHR) fellowships. K. Merritt is funded by a UK Medical Research Council grant (no. MR/S003436/1). R.A. McCutcheon and K. Merritt contributed equally to this paper. Supplementary information on the study is available at https://doi.org/10.5281/zenodo.4739435

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Figure 1 PRISMA flow chart

Table 1 Studies investigating striatal dopamine in individuals at high clinical and genetic risk for psychosis

	Study	Probands				Controls		PET tracer
		N	Age (yrs., mean)	At-risk group	Antipsychotic treatment	N	Age (yrs., mean)	
PRESYNAPTIC DDOPAMINERGIC FUNCTION	Huttunen et al[49]	17	34.1	FDR	All naïve	17	33.0	^{18}F-DOPA
	Brunelin et al[28]	8	28.5	FDR	All naïve	10	27.7	^{11}C-raclopride + metabolic stress
	Shotbolt et al[27]	7	43.0	1 MZ, 6 DZ	All naïve	20	39.0	^{18}F-DOPA
	Kasanova et al[50]	16	42.4	FDR	All naïve	16	38.1	^{18}F-fallypride + reward task
	van Duin et al[51]	12	33.1	22q	All naïve	16	38.1	^{18}F-fallypride + reward task
	Rogdaki et al[52]	21	26.1	22q	All naïve	26	26.1	^{18}F-DOPA
	Abi-Dargham et al[43]	13	36.0	SPD	Free for ≥21 days	13	34.0	[^{123}I] IBZM + AMPH
	Howes et al[18]	30	24.2	CHR	All naïve	29	25.6	^{18}F-DOPA
	Egerton et al[44]	26	22.7	CHR	24 free/naïve, 2 medicated	20	24.5	^{18}F-DOPA
	Bloemen et al[45]	14	22.0	CHR	All free and less than 1 week lifetime use	15	22.2	[^{123}I]IBZM +AMPT
	Tseng et al[46]	24	23.6	CHR	All naïve	25	25.1	[^{11}C]-(+)-PHNO + MIST
	Howes et al[42]	51	23.0	CHR	All naïve	19	25.1	^{18}F-DOPA
	Girgis et al[47]	14	22.4	CHR	All free	14	22.7	[^{11}C]-(+)-PHNO + AMPH
	Thompson et al[48]	16	37.4	SPD	All naïve	16	37.0	^{11}C-raclopride + AMPH
D2/D3 RECEPTOR AVAILABILITY	Hirvonen et al[54]	11	50.2	6 MZ, 5 DZ	All naïve	13	51.5	^{11}C-raclopride
	Lee et al[55]	11	25.1	2 MZ, 9 FDR	All naïve	11	25.5	^{11}C-raclopride
	Brunelin et al[28]	8	27.7	FDR	All naïve	10	28.5	^{11}C-raclopride
	van Duin et al[51]	12	33.1	22q	All naïve	16	38.1	^{18}F-fallypride
	Vingerhoets et al[53]	15	28.2	22q	All naïve	11	26.6	[^{123}I]IBZM
	Abi-Dargham et al[43]	13	36.0	SPD	Free for ≥21 days	13	34.0	[^{123}I]IBZM
	Tseng et al[46]	24	23.6	CHR	All naïve	25	25.1	[^{11}C]-(+)-PHNO
	Vingerhoets et al[53]	16	23.1	CHR	All naïve	11	26.6	[^{123}I]IBZM
	Girgis et al[47]	14	22.4	CHR	All free	14	22.7	[^{11}C]-(+)-PHNO
	Thompson et al[48]	16	37.4	SPD	All naïve	16	37.0	^{11}C-raclopride

CHR – clinical high risk, FDR – first degree relatives, MZ – monozygotic twins, DZ – dizygotic twins, 22q – 22q11 deletion syndrome, SPD – schizotypal disorder, AMPH – dextroamphetamine, AMPT – alpha-methyl-paratyrosine depletion, MIST – Montreal Imaging Stress Test, IBZM – I-(S)-2-hydroxy-3-iodo-6-methoxy-N-[1-ethyl-2-pyrrodinyl)-methyl]benzamide

Figure 2 Forest plots of studies investigating standardized mean differences of measures of dopamine and glutamate in individuals at genetic and clinical high risk for psychosis. SMD – standardized mean difference (Hedges' g), CHR – clinical high risk, GHR – genetic high risk, Da – dopamine, Glu – glutamate, Glx – glutamate + glutamine; K – number of studies.

Figure 3 Forest plots of studies investigating variability differences of measures of dopamine and glutamate in individuals at genetic and clinical high risk for psychosis. CVR – coefficient of variation, CHR – clinical high risk, GHR – genetic high risk, Da – dopamine, Glu – glutamate, Glx –glutamate + glutamine, K – number of studies.

Table 2 Studies investigating glutamate function in individuals at high clinical and genetic risk for psychosis

	Study	Probands				Controls		Substance measured
		N	Age (yrs., mean)	At-risk group	Antipsychotic (AP) treatment	N	Age (yrs., mean)	
Prefrontal cortex	Byun et al[58]	20	21.8	CHR	N=8 low-dose AP	20	22.0	Glx
	Natsubori et al[59]	24	21.7	CHR	N=10 taking AP	26	22.3	Glx
	Egerton et al[56]	75	23.3	CHR	N=3 taking AP	55	24.6	Glu, Glx
	de la Fuente-Sandoval et al[60]	23	21.4	CHR	All naïve	24	20.7	Glx
	Liemburg et al[61]	16	23.0	CHR	All naïve	36	27.1	Glx
	Wang et al[62]	21	21.1	CHR	All naïve	23	22.5	Glx
	Menschikov et al[33]	21	20.2	CHR	NS	26	20.2	Glx
	Modinos et al[57]	21	23.7	CHR	All naïve	20	22.2	Glu, Glx
	Da Silva et al[63]	35	21.3	CHR	All naïve	18	20.6	Glx
	Wenneberg et al[35]	119	23.9	CHR	N=57 naïve, N=44 free	58	25.3	Glu, Glx
	Block et al[74]	35	49.2	FDR, SDR	All naïve	19	40.2	Glx
	Tibbo et al[70]	20	16.4	FDR	All naïve	22	16.7	Glx
	Purdon et al[71]	15	46.3	FDR	All naïve	14	43.5	Glu, Glx
	Yoo et al[75]	22	22.6	FDR	All naïve	22	23.1	Glx
	Lutkenhoff et al[72]	12	49.5	FDR	All naïve	21	55.7	Glu
	Da Silva et al[76]	7	28.5	22q	All naïve	23	31.2	Glu, Glx
	Capizzano et al[77]	24	19.5	FDR, SDR	All naïve	20	20.2	Glx
	Tandon et al[78]	23	15.9	FDR	All naïve	24	15.6	Glx
	Rogdaki et al[31]	20	28.6	22q	N=2 taking AP	30	27.6	Glx
	Vingerhoets et al[73]	17	30.7	22q	All naïve	20	34.2	Glu
	Legind et al[32]	44	42.2	FDR	NS	85	41.2	Glu, Glx
Hippocampus	Stone et al[64]	24	25.0	CHR	N=6 taking AP	27	25.0	Glu, Glx
	Bloemen et al[65]	11	21.3	CHR	NS	11	22.2	Glu
	Nenadic et al[66]	31	23.7	CHR	All naïve	42	23.8	Glu
	Shakory et al[67]	25	22.2	CHR	N=6 low-dose AP	31	21.0	Glu, Glx
	Bossong et al[30]	86	24.7	CHR	N=10 taking AP, N=4 previous AP	30	22.4	Glu, Glx
	Wood et al[68]	61	19.2	CHR	All naïve	25	21.1	Glx
	Provenzano et al[34]	44	21.2	CHR	NS	13	23.3	Glx
	Lutkenhoff et al[72]	12	49.5	FDR	All naïve	21	57.3	Glu
	Da Silva et al[76]	7	28.5	22q	All naïve	16	31.2	Glu, Glx
	Capizzano et al[77]	35	19.4	FDR, SDR	All naïve	24	20.2	Glx
	Rogdaki et al[31]	23	28.6	22q	N=2 taking AP	17	27.6	Glx
Basal ganglia	de la Fuente Sandoval et al[69]	18	19.6	CHR	All naïve	40	21.8	Glu, Glx
	de la Fuente Sandoval et al[60]	23	21.4	CHR	All naïve	24	20.7	Glx
	Block et al[74]	35	49.2	FDR, SDR	All naïve	19	40.2	Glx
	Keshavan et al[79]	40	15.6	FDR	All naïve	48	15.6	Glx
	Tandon et al[78]	23	15.9	FDR	All naïve	24	15.6	Glx
	Thakkar et al[80]	23	31.2	FDR	All naïve	24	33.9	Glx
	Rogdaki et al[31]	17	28.6	22q	N=2 taking AP	30	27.6	Glx
	Vingerhoets et al[73]	20	30.7	22q	All naïve	16	34.2	Glu
Thalamus	Byun et al[58]	20	21.8	CHR	N=8 low-dose AP	20	22.0	Glx
	Egerton et al[56]	75	23.3	CHR	N=3 taking AP	55	24.6	Glu, Glx
	Wenneberg et al[35]	105	23.9	CHR	N=57 naïve, N=44 free	55	25.3	Glu, Glx
	Tandon et al[78]	23	15.9	FDR	All naïve	24	15.6	Glx
	Legind et al[32]	48	42.2	FDR	All naïve	88	41.2	Glu, Glx
	Yoo et al[75]	22	22.6	FDR	All naïve	22	23.1	Glx
	Rogdaki et al[31]	20	28.6	22q	N=2 taking AP	29	27.6	Glx

CHR – clinical high risk, FDR – first-degree relative, SDR – second-degree relative, 22q – 22q11 deletion syndrome, NS – not specified, Glu - glutamate, Glx – glutamate + glutamine

Figure 4 Meta-regressions of standardized mean differences against study level variables