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Cerebrospinal fluid monoamine metabolite concentrations as intermediate phenotypes between glutamate-related genes and psychosis

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ABSTRACT

Glutamate-related genes have been associated with schizophrenia, but the results have been ambiguous and difficult to replicate. Homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) are the major degradation products of the monoamines dopamine, serotonin and noradrenaline, respectively, and their concentrations in the cerebrospinal fluid (CSF), mainly HVA, have been associated with schizophrenia. In the present study, we hypothesized that CSF HVA, 5-HIAA and MHPG concentrations represent intermediate phenotypes in the association between glutamate-related genes and psychosis. To test this hypothesis, we searched for association between 238 single nucleotide polymorphisms (SNPs) in ten genes shown to be directly or indirectly implicated in glutamate transmission and CSF HVA, 5-HIAA and MHPG concentrations in 74 patients with psychotic disease. Thirty-eight nominally significant associations were found. Further analyses in 111 healthy controls showed that 87% of the nominal associations were restricted to the patients with psychosis. Some of the psychosis-only-associated SNPs found in the D-amino acid oxidase activator (DAOA) and the kynurenine 3-monooxygenase (KMO) genes have previously been reported to be associated with schizophrenia. The present results suggest that CSF monoamine metabolite concentrations may represent intermediate phenotypes in the association between glutamate-related genes and psychosis.

1. Introduction

Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS) and several lines of evidence suggest association between the glutamatergic system and schizophrenia (Cherlyn et al., 2010). Several glutamate-related genes have been associated with schizophrenia, however the results have been difficult to replicate in subsequent studies until recently, when a genome wide association study of more than 100,000 individuals found association between genes related to glutamatergic neurotransmission and the disorder (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

Homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) are the major degradation products of the monoamines dopamine, serotonin and noradrenaline, respectively, and their concentrations in the cerebrospinal fluid (CSF) are considered to reflect the turnover rates of the monoamines in the CNS (Stanley et al., 1985; Wester et al., 1990). Several lines of evidence suggest connections and interactions in CNS between glutamate and the monoamine systems, mainly dopamine. Dopamine regulates the activity of glutamatergic neurons in cortex, where as glutamatergic neurons innervate dopamine cells in ventral tagmental area (Sesack et al., 2003). Moreover, dopamine and glutamate modulate common target neurons in various brain regions, including prefrontal cortex and basal ganglia (Sesack et al., 2003). Glutamate is co-released

from the majority of serotonergic neurons in raphe nuclei (Fischer et al., 2014) and serotonin reuptake inhibitors modulate glutamate synapses onto serotonergic neurons of the dorsal raphe nucleus (Geddes et al., 2015). A synergistic regulation of glutamatergic neurotransmission in cortex by the serotonin and norepinephrine systems has also been reported (Yuen et al., 2014). Finally, the CSF concentration of kynurenic acid, a glutamate receptor antagonist (Schwarcz et al., 2012), has been reported to have positive inter-correlations with both CSF HVA and 5-HIAA (Nilsson et al., 2007).

Investigating the association between gene variants and inter-mediate phenotypes in psychotic individuals is a powerful approach that can result in more robust results as well as a deeper understanding of the genotype-phenotype associations (Freimer and Sabatti, 2003; Bilder et al., 2009). An intermediate phenotype can be defined as a mechanism-related manifestation of a complex phenotype, in our case the psychotic disorder (Goldman and Ducci, 2007). An endophenotype should meet specific criteria, i.e. heritability, disease association, state-independence and co-segregation within families (Gottesman and Gould, 2003). Moreover, for complex diseases, such as schizophrenia, it has been proposed that an endophenotype should be found at a higher rate in non-affected family members relative to general population (Gottesman and Gould, 2003).

The term intermediate phenotype is used by many authors for traits that have not been formally shown to meet the criteria for endophenotypes (Goldman and Ducci, 2007). In the present study, we have used the term intermediate phenotypes to characterize the monoamine metabolite concentrations relative to psychosis, as they have been reported to be heritable and to some extend psychosis-related, but do not formally fulfill all the endophenotype-related criteria required.

Regarding heritability, a study in human twins has shown that CSF MHPG is under major genetic influence, whereas CSF 5-HIAA and HVA are under both genetic and environmental influence (Oxenstierna et al., 1986). Studies in other primates also indicate that monoamine metabolite CSF concentrations are partially under genetic influence (Higley et al., 1993; Rogers et al., 2004). Regarding disease association, schizophrenia has been associated with monoamine metabolite concentrations, mainly HVA. HVA concentrations have been reported to be significantly lower in drug-free patients with schizophrenia compared to controls (Bjerkenstedt et al., 1985; Lindström, 1985; Wieselgren and Lindstrom, 1998). Increased CSF MHPG concentrations have also been associated with psychosis (Hsiao et al., 1993).

N-methyl-ᴅ-aspartate receptors (NMDARs), one of the main glutamate receptor classes, play a critical role in neurodevelopment, learning and memory (Hirasawa et al., 2003; Riedel et al., 2003). It has been proposed that a hypofunction of the NMDARs is implicated in the pathophysiology of schizophrenia, generating cognitive, negative and positive symptoms (Javitt and Zukin, 1991; Krystal et al., 1994; Javitt, 2008; Labrie and Roder, 2010). In the present study, we chose two genes encoding NMDAR subunits, i.e. glutamate receptor, ionotropic, N-methyl-ᴅ-aspartate, subunit 1 (GRIN1) encoding the NR1 subunit and glutamate receptor, ionotropic, N-methyl-ᴅ-aspartate, subunit 2B (GRIN2B) encoding the NR2B subunit, being the most studied NMDAR subunits-related genes in schizophrenia. (www.szgene.org). GRIN1 and GRIN2B are located on chromosomes 9q34.3 and 12p12, respectively.

The ᴅ-amino acid oxidase activator (DAOA) protein is located in various regions of CNS, mainly amygdala and nucleus caudatus (Chumakov et al., 2002). DAOA regulates the function of ᴅ-amino acid oxidase (DAO), a flavoprotein catalyzing the oxidative deamination of ᴅ-amino acids, including ᴅ-DOPA and ᴅ-serine, a co-agonist of the NMDARs (Wu et al., 2006; Kawazoe et al., 2007). The DAO gene is located on chromosome 12q24, whereas the DAOA gene is located on chromosome 13q34.

Disrupted in schizophrenia 1 (DISC1) is a protein, involved in neurodevelopment, plasticity and migration of neurons (Thomson et al., 2013). It affects glutamate neurotransmission in several ways, mainly by modulating serine racemase, an enzyme that generates ᴅ-serine, altering the NMDAR neurotransmission (Snyder and Gao, 2013). The DISC1 gene is located on chromosome 1q42.1.

Brain-derived neurotrophic factor (BDNF) is the most expressed neurotrophic factor in the brain and is considered to play an important role in the development, survival and regeneration of neurons (Balaratnasingam and Janca, 2012; Nurjono et al., 2012). BDNF is implicated in the glutamatergic as well as dopamine and serotonergic neurotransmitter systems (Nurjono et al., 2012). The BDNF gene is located on chromosome 11p13.

Dysbindin is a protein implicated in synaptic structure and signaling, as well as in neurodevelopment (Benson et al., 2001; Ghiani et al., 2010). It is involved in both dopamine and glutamate neurotransmission in CNS (Talbot et al., 2004; Weickert et al., 2004). Dysbindin is encoded by the dystrobrevin-binding protein 1 (DTNBP1) gene, located on chromosome 6p22.3.

Indoleamine 2,3-dioxygenase (IDO), tryptophan 2,3-dioxygenase (TDO) and kynurenine 3-monooxygenase (KMO) are important enzymes implicated in the kynurenine pathway of tryptophan degradation (Schwarcz et al., 2012). Kynurenic acid and other neuroactive metabolites of this pathway are implicated in gluta-matergic, dopaminergic and noradrenergic neurotransmissions (Myint and Kim, 2014). Dysregulation of the kynurenine pathway has also been associated with mental disorders, mainly schizophrenia (Schwarcz et al., 2012). IDO, TDO and KMO are encoded by the IDO1, TDO2 and KMO genes, located on chromosomes 8p12-p11, 4q31-q32 and 1q42-q44, respectively.

In the present study, we considered the major metabolites of dopamine, serotonin, and noradrenaline as intermediate steps between glutamate-related genes and psychosis. We hypothesized that single nucleotide polymorphisms (SNPs) in these genes affect the CSF concentrations of HVA, 5-HIAA, and MHPG in psychotic patients.

2. Methods

2.1. Subjects

Patients with psychosis, recruited among inpatients from four psychiatric university clinics in Stockholm County between the years 1973 and 1987, were asked to participate in pharmacological and/or biological research projects (Bjerkenstedt et al., 1977; Wode-Helgodt et al., 1977; Härnryd et al., 1984; Oxenstierna et al., 1996). All participants were observed for at least 48 hours without any antipsychotic medication and CSF samples were drawn by a lumbar puncture.

Seventy-four psychotic patients (45 men and 29 women) participated in the present study. The mean age (standard deviation) at lumbar puncture was 30.4 (7.2) years, whereas the mean age of disease onset (standard deviation) was 27.6 (7.8) years. Thirty-five percent of the patients (N=26) were treated with antipsychotic medication, whereas 49% (N=36) were free from antipsychotics since three weeks or more. Sixty-four patients were diagnosed with schizophrenia spectrum disorder (schizophrenia n=60 and schizoaffective disorder n=4), whereas ten patients were diagnosed with other psychosis (psychosis not otherwise specified (NOS) n=7, delusional disorder n=1, bipolar disorder n=1, alcohol induced psychotic disorder n=1).

Three to 34 years after the first investigation, the psychotic patients were asked to participate in genetic research studies and whole blood was drawn for genotyping. The participants were asked to undergo a structured interview (Spitzer et al., 1988) and permit the researchers to retrieve their medical records. Available records were scrutinized by researchers in order to obtain a life-time diagnosis according to DSM-III-R and DSM-IV. In 2010, hospital discharge diagnoses were obtained from the Swedish psychiatric inpatient register (SPIR), a register covering all inpatient hospitalizations in Sweden since 1973. Psychiatric diagnoses were recorded for each hospitalization according to the International Classification of Diseases, 8th, 9th or 10th revisions. Most patients had experienced several hospitalizations. However, each patient obtained one diagnosis, following a diagnostic hierarchy (Ekholm et al., 2005; Vares et al., 2006). The final diagnoses were based

on the SPIR, as it was not possible to retrieve medical records from all patients and some of the patients were not willing to participate in a diagnostic interview.

These 74 patients have been also included in a recent study, searching for association between genes encoding enzymes implicated in monoamine metabolism and CSF monoamine metabolite concentrations (Andreou et al., 2014).

For SNPs that were nominally associated with CSF HVA, 5-HIAA or MHPG concentrations in psychotic patients, analyses in healthy subjects were performed, in order to evaluate whether the effects of the associated SNPs were restricted to the patients. Healthy unrelated Caucasians ($n=111$; 63 men and 48 women) were included in the study for that purpose. CSF samples were drawn by lumbar puncture between 1973 and 1987. Eight to 20 years after this first investigation, the healthy controls were interviewed to re-assess the absence of psychiatric morbidity (Jönsson et al., 2004) and whole blood was drawn for genotyping.

Some or all of the 111 controls have previously participated in studies searching for association between gene variants and CSF monoamine metabolite concentrations in healthy individuals only (Jönsson et al., 1996, 1997, 1998, 2000; Damberg et al., 2004; Jönsson et al., 2004, 2008; Andreou et al., 2010; Annerbrink et al., 2010; Andreou et al., 2011, 2012). Recently, the 111 controls were included in a study searching for association between genes implicated in monoamine metabolism and CSF monoamine metabolite concentrations in psychotic patients and healthy individuals (Andreou et al., 2014).

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Karolinska University Hospital. Written informed consent was obtained from all participants.

2.2. CSF monoamine metabolite concentrations

12.5 ml CSF was drawn by lumbar puncture from all subjects between 8 and 9 a.m. after at least 8 h of bed-rest and absence of food intake or smoking. All participants were in a sitting or recumbent position during the procedure. 5-HIAA, HVA, and MHPG CSF concentrations were measured by mass fragmentography with deuterium-labeled internal standards (Swahn et al., 1976).

2.3. DNA analysis

Genomic DNA was extracted from whole blood (Geijer et al., 1994). Totally, 238 SNPs were genotyped from 10 genes, i.e. GRIN1 ($n=10$), GRIN2B ($n=5$), DAOA ($n=19$), DAO ($n=11$), DISC1 ($n=122$), BDNF ($n=10$), DTNBP1 ($n=26$), KMO ($n=25$), IDO1 ($n=3$) and TDO2 ($n=7$). These SNPs were either candidate SNPs ($n=42$) previously associated with schizophrenia, other mental disorders, monoamine metabolite concentrations or having other known functionality, or tag-SNPs ($n=196$), selected using HapMap to cover the ten genes with an r^2 threshold of 0.8. The genotyping was performed using the Illumina BeadStation 500GX and the 768-plex Illumina Golden Gate assay (Illumina Inc., San Diego, CA, USA) (Fan et al., 2003).

2.4. Statistical analysis

Hardy–Weinberg equilibrium (HWE) was tested using exact significance as implemented in STATA 12.1. Minor allele frequencies were measured and normality of residuals was checked graphically with STATA 12.1. The associations between SNPs and HVA, 5-HIAA and MHPG CSF concentrations were tested by multiple linear regression (STATA 12.1), where concentration was modeled as a linear function of the allele count (of each SNP separately) and three to five covariates.

In the analyses of psychotic patients, gender, age at lumbar puncture, back-length, diagnosis (i.e. schizophrenia spectrum psychosis or other psychosis) and antipsychotic treatment were included as covariates. Antipsychotic treatment was regarded as present if patients had taken antipsychotic medication during a three-week period prior to the lumbar puncture. In the case of healthy controls, back-length, gender and age at lumbar puncture were used as covariates.

In patients with psychosis, we conducted 714 tests, as we have tested 238 SNPs separately for each of the three monoamine metabolites. Adjustments for multiple testing were performed using a Bonferroni correction taking into account the number of tests conducted ($\alpha=7 \times 10^{-5}$).

3. Results

SNPs ($n=238$) in ten genes were genotyped in psychotic patients. The minor allele frequencies for the selected markers ranged from 0% to 50%. The mean (standard deviation) concentrations of the three monoamine metabolites were: HVA 178.6 (79.3) nmol/L; 5-HIAA 93.1 (34) nmol/L; MHPG 43.3 (9.3) nmol/L.

Thirteen, 16 and nine of the genotyped SNPs (Tables 1–3) were nominally associated with CSF HVA, 5-HIAA and MHPG

Table 1
Minor allele frequencies (MAF), p-values for Hardy–Weinberg equilibrium tests (HWE) and p-values (P) from nominal associations between single nucleotide polymorphisms (SNPs) and cerebrospinal fluid homovanillic acid (HVA) concentrations in psychotic patients. Corresponding association statistics among healthy controls.

Gene	SNP	Patients with psychosis ($n=74$; 45 men, 29 women)			Healthy controls ($n=111$; 63 men, 48 women)		
		HVA mean (S.D.) 178.6 (79.3) nmol/l			167.5 (68.4) nmol/l		
		MAF (%)	HWE	P	MAF (%)	HWE	P
DISC1	rs12046794	11	0.590	0.001	9	0.173	0.435
DISC1	rs1934909	14	1.000	0.007	14	0.123	0.964
DISC1	rs10158776	2	1.000	0.013	1	1.000	0.970
IDO1	rs6991530	14	1.000	0.015	14	1.000	0.290
DAO	rs17041020	7	1.000	0.021	5	1.000	0.040
DISC1	rs823162	7	0.042	0.022	5	1.000	0.402
DISC1	rs4325116	39	0.462	0.034	37	0.838	0.904
DISC1	rs4385690	18	1.000	0.038	24	0.203	0.717
DAOA	rs1421292	43	0.344	0.040	42	0.561	0.006
DISC1	rs1322783	12	0.277	0.043	15	0.280	0.878
DAOA	rs3916971	47	0.066	0.045	47	0.849	0.009
DISC1	rs16854967	14	0.609	0.049	14	0.468	0.925
DAO	rs2070586	14	1.000	0.049	19	0.355	0.790

Table 2
Minor allele frequencies (MAF), p-values for Hardy–Weinberg equilibrium tests (HWE) and p-values (P) from nominal associations between single nucleotide polymorphisms (SNPs) and 5-hydroxyindoleacetic acid (5-HIAA) cerebrospinal fluid concentrations in psychotic patients. Corresponding association statistics among healthy controls.

Gene	SNP	Patients with psychosis ($n=74$; 45 men, 29 women)			Healthy controls ($n=111$; 63 men, 48 women)		
		5-HIAA mean (S.D.) 93.1 (34) nmol/l			90.8 (36.2) nmol/l		
		MAF (%)	HWE	P	MAF (%)	HWE	P
DAOA	rs3918342	47	0.647	0.002	46	0.703	0.072
DISC1	rs1934909	14	1.000	0.010	14	0.123	0.400
DAOA	rs1421292	43	0.344	0.010	42	0.561	0.085
DISC1	rs1331056	45	0.154	0.012	40	0.844	0.131
DAOA	rs3916971	47	0.066	0.018	47	0.849	0.093
GRIN1	rs28489906	47	0.100	0.025	48	1.000	0.500
KMO	rs1932441	29	0.395	0.026	36	0.680	0.093
IDO1	rs6991530	14	1.000	0.028	14	1.000	0.194
DISC1	rs2806465	50	0.062	0.033	45	0.443	0.033
KMO	rs12410855	36	0.079	0.034	36	0.681	0.946
DAOA	rs778293	43	0.237	0.034	42	1.000	0.049
DISC1	rs12046794	11	0.590	0.035	8	0.484	0.365
DISC1	rs17820909	10	1.000	0.036	6	1.000	0.597
DTNBP1	rs12525702	9	0.438	0.040	8	0.115	0.250
DTNBP1	rs3829893	11	0.031	0.042	10	0.321	0.656
DISC1	rs9726024	34	0.606	0.048	34	0.403	0.158

concentrations, respectively. The residuals of the nominal associations were approximately normally distributed. Two of the associated SNPs, i.e. DISC1 rs823162 and DTNBP1 rs3829893, showed departure from Hardy–Weinberg equilibrium (p-value < 0.05) (Tables 1 and 2). Taking into account the total number of tests conducted, we applied a Bonferroni correction ($\alpha=0.05/714=7 \times 10^{-5}$) and none of the nominal associations remained significant.

In order to evaluate how the Swedish in-patient resister-based diagnoses, which were used as our final diagnoses in the present study, conformed to other diagnostic tools, separate analyses were performed. Data from medical records were retrieved for 52 of the

Table 3
Minor allele frequencies (MAF), *p*-values for Hardy–Weinberg equilibrium tests (HWE) and *p*-values (*P*) from nominal associations between single nucleotide polymorphisms (SNPs) and 3-methoxy-4-hydroxyphenylglycol (MHPG) cerebrospinal fluid concentrations in psychotic patients. Corresponding association statistics among healthy controls.

Gene	SNP	Patients with psychosis (*n*=74; 45 men, 29 women)			Healthy controls (*n*=111; 63 men, 48 women)		
		MHPG mean (S.D.) 43.3 (9.3) nmol/l			41.7 (8.1) nmol/l		
		MAF (%)	HWE	*P*	MAF (%)	HWE	*P*
KMO	rs2275163	39	0.808	0.003	35	0.290	0.965
KMO	rs4660103	33	1.000	0.003	29	0.242	0.558
KMO	rs6677357	28	1.000	0.005	26	0.622	0.877
DISC1	rs1934909	14	1.000	0.015	14	0.123	0.574
KMO	rs12138459	27	0.769	0.024	28	0.485	0.938
DISC1	rs2812385	42	0.474	0.026	28	1.000	0.775
DAOA	rs1570709	22	0.165	0.026	22	0.096	0.447
IDO1	rs7010461	35	0.619	0.028	29	0.167	0.952
KMO	rs2050516	47	0.647	0.044	40	0.691	0.714

patients, resulting in a diagnosis of a psychotic disorder in 98% of these individuals. Forty-four patients participated in a diagnostic interview (Spitzer et al., 1988) and 91% of these patients displayed a psychotic disorder according to the SCID-I algorithm. These results are in accordance with previous studies reporting that SPIR-derived diagnoses of schizophrenia spectrum psychosis have a high validity, as 85–94% of the patients received these diagnoses when diagnostic evaluations were made using information from medical records and a structured clinical interview (Vares et al., 2006).

The mean CSF MHPG concentration was significantly lower in patients who were prescribed antipsychotics relative to antipsychotic-free patients, whereas mean CSF HVA and 5-HIAA concentrations were not found to be associated with antipsychotic treatment. As we have included the use of antipsychotics as a covariate in our analyses and moreover, our independent variables, i.e. the SNPs, are not expected to be associated with the presence or absence of antipsychotic treatment, we consider that the use of antipsychotics should not confound our analyses, even in the case of MHPG.

The nominal associations (*n*=38) between SNPs and monoamine metabolite concentrations in psychotic patients were tested separately in 111 healthy unrelated individuals in order to find out whether these nominal associations were restricted to psychotic patients or were also present in controls. The mean (standard deviation) concentrations of the three monoamine metabolites were: HVA 167.5 (68.4) nmol/L; 5-HIAA 90.8 (36.2) nmol/L; MHPG 41.7 (8.1) nmol/L. The minor allele frequency for the selected markers ranged from 1% to 48% (Tables 1–3). No SNPs showed deviation from the Hardy–Weinberg principles (Tables 1–3). The residuals were approximately normally distributed. Three and two nominal associations were found between SNPs and HVA and 5-HIAA, respectively in controls, whereas the majority of the nominal associations (*n*=33) were restricted to patients with psychosis.

Additional analysis was conducted, investigating whether the nominally significant associations found in psychotic patients were preserved in the drug-free psychotic patients. We found that 46% of the associations remained nominally significant. More specifically, 8/12, 6/16 and 3/9 of the nominal associations between SNPs and HVA, 5-HIAA and MHPG, respectively, were preserved.

4. Discussion

4.1. General considerations

To our knowledge, no other studies have searched for associations between gene variants and CSF monoamine metabolite concentrations in patients with psychosis, with one exception. We reported nominal associations between genes encoding enzymes implicated in the monoamine metabolism and CSF monoamine metabolite concentrations in psychosis (Andreou et al., 2014). Almost all the nominal associations were absent in healthy controls. One of the investigated genes was the *MAOB* gene, located on chromosome Xp11.23 and encoding the enzyme monoamine oxidase B. Monoamine oxidases play an important role in the degradation of biogenic amines, including dopamine, noradrenaline and serotonin (Shih et al., 1999). The intronic *MAOB* SNP rs5905512, applying a less conservative correction for multiple testing,was found to be significantly associated with MHPG concentrations in psychotic men only, suggesting that a previously reported association between this intronic SNP and schizophrenia in men only (Carrera et al., 2009), may be mediated by noradrenergic mechanisms. The participants in the present study and in the study investigating the above named genes were the same, i.e. 74 patients with psychosis and 111 healthy individuals.

One main reason why the term intermediate phenotype has been used throughout the present article instead for the term endophenotype is the fact that the CSF monoamine metabolite concentrations in patients with schizophrenia have been found to be affected by a variety of factors, including the clinical state of the disorder, the patients' characteristics and the medication with antipsychotics and thus cannot be considered as state independent. Global Assessment Scale scores, reflecting the clinical state of the disorder, were negatively correlated with CSF HVA concentrations in drug-free patients with schizophrenia (Houston et al., 1986). CSF 5-HIAA concentrations have been associated with negative and disorganization dimensions (Anand et al., 2002), deficit characteristics (Csernansky et al., 1990), hallucinations (Gattaz et al., 1982) and delusions (Lindström, 1985). CSF HVA concentrations have been associated with the psychosis dimension in first episode drug naive patients with schizophrenia (Anand et al., 2002) as well as the patients' social interest (Lindström, 1985). Regarding antipsychotics, quetiapine and olanzapine administration have been found to be associated with a significant increase in CSF HVA (Scheepers et al., 2001; Nikisch et al., 2010). Moreover, the correlation between HVA and 5-HIAA, found to be almost linear in healthy individuals, was substantially lower in untreated psychotic patients relative to controls and was normalized after treatment with antipsychotics (Hsiao et al., 1993).

The majority of the nominally significant associations found in psychotic patients were absent in healthy controls. When we restricted the analysis to the smaller group of patients not taking antipsychotics approximately half of the nominal associations were preserved. The decrease of nominal associations from 37 to 17 is likely a result of a decrease in power due to the decrease in the number of individuals included in the analysis.

4.2. GRIN1, GRIN2B, DAOA and DAO

*GRIN*1 has been associated with schizophrenia in four out of 15 studies conducted (www.szgene.org), as well as with bipolar disorder (Mundo et al., 2003). In the present study, one intronic *GRIN*1 SNP, i.e. rs28489906, was associated with 5-HIAA concentrations in psychotic patients and to our knowledge, this SNP has not been ascribed any functionality or association with mental disorders.

*GRIN*2B has been associated with schizophrenia in 5/13 studies

conducted (www.szgene.org), as well as with bipolar disorder (Martucci et al., 2006), autistic spectrum disorder (Yoo et al., 2012) and attention deficit hyperactivity disorder (Dorval et al., 2007). The product of the *GRIN2B* gene, i.e. the NR2A subunit has been reported to have reduced expression in the prefrontal cortex in patients with major depression compared to controls (Feyissa et al., 2009). No *GRIN2B* SNPs were associated with monoamine metabolite concentrations in the present study.

DAOA has been associated with schizophrenia in 27/41 studies with two positive meta-analyses (www.szgene.org), as well as with major depression (Rietschel et al., 2008) and bipolar disorder (Prata et al., 2008). *DAOA* has also been associated with response to antipsychotic treatment (Pae et al., 2010) and progression of prodromal syndromes to first episode psychosis (Mossner et al., 2010). Moreover, *DAOA* transgenic mice showed psychosis-associated behavioral phenotypes that could be reversed by haloperidol (Otte et al., 2009). In the present study two, four and one *DAOA* SNPs were nominally associated with CSF concentrations of HVA, 5-HIAA and MHPG, respectively Tables 1–3).

DAOA rs3918342 has been associated with schizophrenia and bipolar disorder (Korostishevsky et al., 2004; Schumacher et al., 2004; Bass et al., 2009; Ma et al., 2009). This SNP has been reported to modulate hippocampal and prefrontal cortex function in subjects at high risk of schizophrenia (Hall et al., 2008). *DAOA* rs778293 has also been associated with schizophrenia in independent studies (Korostishevsky et al., 2004; Ma et al., 2006, 2009) and a meta-analysis (Shi et al., 2008) as well as with methamphetamine psychosis (Kotaka et al., 2009) and bipolar disorder (Zhang et al., 2009). In the present study, rs3918342 and rs778293 were nominally associated with 5-HIAA concentrations in psychotic patients. Rs778293 was also associated with 5-HIAA in controls, whereas the association between rs3918342 and 5-HIAA was restricted to psychosis. We can therefore hypothesize that an altered serotonin turnover rate in CNS, as reflected by the CSF 5-HIAA concentration, may be an intermediate phenotype in the previously reported association between rs3918342 and schizophrenia. Rs3918342 showed the lowest *p*-value (0.002) in association with 5-HIAA concentrations in psychotic patients in the present study and is located 28 Kb downstream of the *DAOA* gene.

DAOA rs1421292 has been associated with schizophrenia (Schumacher et al., 2004) and has been reported to modulate brain activation in a verbal fluency task in healthy subjects (Krug et al., 2011). *DAOA* rs3916971 has also been associated with schizophrenia (Korostishevsky et al., 2004) with a positive meta-analysis (www.szgene.org). In the present study, rs1421292 and rs3916971 were associated with both CSF HVA and 5-HIAA in patients with psychosis. Both SNPs were also associated with HVA in healthy individuals, where as their associations with 5-HIAA were restricted to psychotic patients, proposing that mainly serotonin turnover in CNS may play a role in the previously reported associations between these SNPs and schizophrenia. Rs1421292 and rs3916971 are located 40 kbp and four kbp downstream of the *DAOA* gene, respectively.

DAOA rs1570709 has been reported to be significantly associated with schizophrenia (Opgen-Rhein et al., 2008). In the present study, rs1570709 was found to be associated with MHPG concentrations in psychotic patients, suggesting that noradrenalin turnover rates in CNS may play a role in the association between the SNP and the disorder.

DAO has been associated with schizophrenia in 6/19 studies (www.szgene.org), as well as with autism spectrum disorders in an independent study (Chung et al., 2007). We found two intronic *DAO* SNPs, i.e. rs2070586 and rs17041020, to be nominally associated with HVA concentrations in psychotic patients. Rs2070586 has previously been reported to be significantly associated with schizophrenia in both men and women (Kim et al., 2010) and our

result supports the notion that this association may be mediated by dopaminergic mechanisms.

4.3. DISC1, BDNF and DTNBP1

*DISC*1 has been associated with schizophrenia in 31/45 studies conducted, as well as with bipolar disorder (Hennah et al., 2009; Schosser et al., 2010) and autism (Zheng et al., 2011). In the present study, eight, six and two SNPs were nominally associated with CSF HVA, 5-HIAA and MHPG concentrations, respectively. To our knowledge, none of these SNPs have been associated with schizophrenia or other mental disorders. All but one of the associated SNPs are related to non coding RNA regions (www.gwascentral. org).

Several lines of evidence have associated BDNF with schizophrenia (Nurjono et al., 2012) and the *BDNF* gene has been associated with the disorder in 11/53 studies conducted (www.szgene. org). *BDNF* SNPs have also been associated with CSF MHPG concentrations in healthy Caucasians (Jönsson et al., 2008). In the present study, no *BDNF* SNPs were associated with HVA, 5-HIAA or MHPG concentrations in patients with psychosis.

*DTNBP*1 has been associated with schizophrenia in 23/62 studies conducted (www.szgene.org) as well as with bipolar disorder (Gaysina et al., 2009) and major depression (Kim et al., 2008). *DTNBP*1 SNPs have also been associated with CSF HVA and 5-HIAA concentrations in healthy humans (Andreou et al., 2011). To our knowledge, no studies have searched for association between *DTNBP*1 gene variants and monoamine metabolite concentrations in schizophrenia. In the present study, two SNPs, i.e. rs12525702 and rs3829893 were associated with CSF 5-HIAA concentrations. These SNPs are related to non coding RNA regions (www.gwas central.org) and have not been associated with mental disorders.

4.4. KMO, IDO1 and TDO2

KMO has been associated with schizophrenia in the first of two independent samples tested in an association study (Aoyama et al., 2006) as well as with psychotic features in bipolar disorder (Lavebratt et al., 2014). In the present study, two *KMO* SNPs, i.e. the intronic rs1932441, and the exonic rs12410855 were associated with CSF 5-HIAA concentrations and five intronic *KMO* SNPs, i.e. rs2275163, rs4660103, rs6677357, rs12138459, rs2050516 were associated with CSF MHPG concentrations in patients with psychosis. One of the SNPs associated with MHPG concentrations, i.e. rs2275163, has been previously associated with schizophrenia in the first of two independent set of samples analyzed (Aoyama et al., 2006) and we could therefore hypothesize that the reported association may be mediated by noradrenergic mechanisms. Interestingly, rs2275163 has been also reported to be associated with visuospatial working memory and predictive pursuit in a combined sample of psychotic patients and controls (Wonodi et al., 2011).

To our knowledge, no candidate gene studies have searched for association between *IDO*1 and schizophrenia and no genome wide association studies have shown evidence of association either. In the present study, rs6991530 was nominally associated with HVA and 5-HIAA, whereas rs7010461 was nominally associated MHPG. To our knowledge, these SNPS have not been associated with mental disorders or ascribed any functionality.

A complex genotype including a *TDO*2 SNP, i.e. rs2271537 and SNPs from two other kynurenine pathway-related genes has been significantly associated with schizophrenia (Miller et al., 2009). However, rs2271537 alone was not associated with the disorder (Miller et al., 2009). Rs2271537 was included as a candidate SNP in the present study and was not associated with CSF HVA, 5-HIAA or MHPG concentrations in psychotic patients.

4.5. Limitations

The major limitation of the present study is the relatively small number of patients and controls relative to the large number of conducted tests. This issue results in a limited power to detect possible associations after correction for multiple testing. Moreover, the associations found need replications in independent studies. Although none of the participating patients took antipsychotics during the last 48 hours prior to lumbar puncture, 35% of the patients were not without antipsychotics during the last three-week period. This is also a limitation of the present study, especially in the associations concerning MHPG, as we have found that the mean CSF MHPG concentration was significantly lower in patients on antipsychotics compared to antipsychotic-free patients.

4.6. Conclusions

In patients with psychosis, we have found nominally significant associations between SNPs in glutamate-related genes and dopamine, serotonin and noradrenaline turnover rates, as reflected by the CSF concentrations of HVA, 5-HIAA and MHPG, respectively. The majority of the nominal associations (87%) were restricted to patients with psychosis and were absent in healthy controls. Moreover, some of the associated SNPs in *DAOA* and *KMO* have been reported to be associated with schizophrenia, proposing that the previously reported associations may be modulated by serotonergic and noradrenergic mechanisms. Taken together, the present results suggest that CSF monoamine metabolite concentrations may represent intermediate phenotypes in the association between glutamate-related genes and psychosis.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DA contributed to the conception and design of the study, participated in subject assessment, subject characterization and the statistical analysis, managed the literature search and web-based database searches and drafted the article. ES performed the statistical analysis. TA was in charge of the genotyping procedures. GCS made a contribution to the conception and design of the study and to the acquisition of data. LT and IA contributed to the conception and design of the study. EGJ contributed to the conception and design of the study, the acquisition and the interpretation of data. All authors revised the article critically for important intellectual content and approved the final manuscript.

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