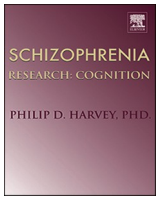
Schizophrenia Research: Cognition 38 (2024) 100321

Contents lists available at ScienceDirect

Schizophrenia Research: Cognition

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



Relationship of cognitive measures to mRNA levels in lymphocytes from patients with schizophrenia and controls

Robert C. Smith [a,b,*], Henry Sershen [a,b], AnMei Chen [c], Hua Jin [d], Alexandro Guidotti [e], John M. Davis [e]

[a] Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, USA
[b] NYU Grossman School of Medicine, Department of Psychiatry, New York, NY, USA
[c] Columbia University Mailman School of Public Health, New York, NY, USA
[d] University of California San Diego, Department of Psychiatry, and VA San Diego Healthcare System, San Diego, CA, USA
[e] The Psychiatric Institute, University of Illinois, Department of Psychiatry, Chicago, IL, USA

ARTICLE INFO

Keywords:
Schizophrenia
Cognition
Lymphocyte mRNA
MATRICS battery

ABSTRACT

Patients with schizophrenia show substantial cognitive deficits and abnormalities in neurotransmitter-related levels of mRNA in brain or peripheral blood lymphocytes. However, the relationship of cognitive deficits as measured by the MATRICS battery and mRNA levels in brain or lymphocytes has not been sufficiently explored. We measured levels of methylation or neurotransmitter-related mRNAs in lymphocytes of 38 patients with chronic schizophrenia (CSZ) and 33 non-psychotic controls (controls) by qPCR using TaqMan probes. We assessed cognitive function in these patients and controls with the MATRICS battery. We used correlation analysis and scatter plots to assess the relationship of lymphocyte mRNA levels to MATRICS domain and composite scores. CSZ subjects had a consistently negative correlation between mRNA levels in lymphocytes and MATRICS cognitive variables of speed of processing, attention-vigilance, working memory, visual learning, and overall composite score. It is uncertain whether these negative correlations represent a causative relation between specific mRNA levels and cognitive deficits. Controls had either positive correlations or non-significant correlations between mRNA and most of the MATRICS variables. There were statistically significant differences in the correlations between mRNA and MATRICS variables between CSZ vs controls for several mRNAs (DNMT1, DNMT3A, BDNF, NR3C1, FPRF3, CNTNAP2). Our data show a different relationship between mRNA levels in peripheral blood lymphocytes and MATRICS cognitive variables in CSZ vs controls. The substantive significance of these differences needs further investigation.

1. Introduction

Patients with schizophrenia show substantial deficits in cognitive function as measured by the MATRICS battery and other neuropsychological tests (Bowie and Harvey, 2006; Green, 1998; Liu et al., 2019). We have previously shown that several mRNAs related to epigenetics regulation, neurotransmitter and cell-cell communication (DNMT, GAD, NR3C1, FPRF3, CNTNAP2) are at significantly different levels in the lymphocytes of patients with chronic schizophrenia compared to controls, and some of these differences have been replicated in post-mortem brain samples (Sershen et al., 2021). The relationship of the levels of these mRNAs in lymphocytes to cognitive function has not been investigated. The current report explores the correlations of MATRICS scores and mRNA levels in lymphocytes in patients with chronic schizophrenia and non-psychotic controls.

2. Methods

2.1. Subjects and study design

The design of the original study, from which data for this paper was drawn, is described in detail in our previous publication (Sershen et al., 2021). Subjects were enrolled in this study and samples collected between 2013 and 2017. Subjects included in the current report were 38 CSZ patients treated with antipsychotic medication, and 33 controls (Table 1). CSZ were recruited from the Nathan Kline Institute (NKI) or its

* Corresponding author at: Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, USA.
E-mail addresses: robert.smith@nki.rfmh.org, robert.smith2@nyumc.org (R.C. Smith).

https://doi.org/10.1016/j.scog.2024.100321
Received 23 January 2024; Received in revised form 24 June 2024; Accepted 25 June 2024

Table 1
Characteristics of subjects.

Characteristic	Schizophrenia - CSZ	Controls	Test
	(*n* = 38)	(*n* = 33)	
Age (m)	46.1 ± 9.3	36.2 ± 11.4	$T = 4.01$, df = 69, $P \leq 0.001$
Sex (M/F) (n)	31/7	22/11	$X^2 = 2.08$, df = 1, $P = .150$
Race (W/B/H/A) (n)	12/22/2/2	7/23/1/2	$X^2 = 1.33$, df = 3, $P = .723$
Cigarette smoker (Y/N) (n)	20/18	6/27	$X^2 = 9.03$, df = 1, $P < .013$
Cigarette smoked/wk. (m)	28.3 ± 44.3	12.7 ± 28.3	$T^u = 1.89$, df = 63.7, $P = .063$
Handedness (right/left)	34/4	32/1	$X^2 = 6.06$, df = 1, $P = .109$
Antipsychotic treatment (1st Gen/2nd Gen/combined) (n)	4/24/10	NR	
On Clozapine (Y/N) (n)	13/25	NR	
On mood stabilizer (Y/N) (n)	15/22	0/48	
On Valproate (Y/N) (n)	7/31	0/48	
On Benzodiazepine (Y/N) (n)	19/19	0/48	
PANSS Total (m)	72.5 ± 16.5	NR	
MATRICS overall composite (m)	21.1 ± 14.0	40.9 ± 9.8	$T^u = 6.83$, df = 62.6, $P < .001$

NR = not relevant; (n) = number of subjects, m = Mean ± S.D., (Y/N) = Yes/No, (P/N) = Positive/Negative, (M/F) = male/female, Race/Ethnicity: W = Caucasian, B = Black or African American, H = Hispanic, A = Asian. Antipsychotic type: 1st Generation antipsychotic, 2nd generation antipsychotic, combined 1st and 2nd Generation antipsychotic. Statistical tests: X^2 = chi-square, FET = Fishers' Exact Test. T = *t*-test. T^u = *t*-test for unequal variances. Data on education level of our subjects was not collected. Cigarettes smoked per week is the subject's response estimate of how many cigarettes they have smoked per week in the last few weeks.

associated state hospital, outpatient clinic, and residences. Control subjects were recruited from the NKI research clinic, or from the local community through advertisements. CSZ (21 outpatients, 17 inpatients) subjects had a long history of illness with several hospitalizations and/or years of outpatient clinic treatment in multiple institutions; available chart records did not provide reliable data to specify precise years of illness or treatment duration. Diagnosis of schizophrenia was made by review of hospital records, using checklists for DSM IV, and later DSM V, and supplemented by SCID diagnostic interviews when these were available from other studies. Controls were subjects who never met criteria for schizophrenia, bipolar disorder, major depressive disorder, schizophreniform disorder, or brief or drug-induced psychosis, and were not currently treated with antipsychotic or antidepressant medication (see supplement for additional details of selection criteria). None of the control subjects were treated with a psychotropic drug for a psychiatric diagnosis. Subjects signed informed consent forms for participation in a protocol approved by the IRB of the Nathan Kline Institute for Psychiatric Research.

2.2. Clinical assessments

Cognitive status was assessed by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery (Nuechterlein et al., 2008) by raters who were trained in the battery's procedures. Psychopathology in CSZ was assessed with the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987) by interview by trained research psychiatrists, or research assistants who had achieved at least an ICC of 0.80 with total PANSS score rating agreement with psychiatrist's ratings.

Table 2-
Gene symbols and TaqMan primers for mRNAs assayed.

Primer probe Gene symbol	Taqman assay Gene expression	Gene name
ACTB	Hs01060665_g1	Actin beta
DNMT1 (custom, cus)	Hs00945875_m1 AIFAT65	DNA (cytosine-5-)-methyltransferase 1 DNMT1 based on primer sequence F: 5′-CGTCTAGAAAACGGGAACCAAGCAAG-3′ R: 5′-TCTAATCCCAGTTACTTGGGAGGCTG-3′
DNMT1 (original, or)	Hs00154749˙m1	DNA (cytosine-5-)-methyltransferase 1 Transcript variant 1 (DNMT1b), 2 (DNMT1a), and variants 3,4
DNMT3A	Hs01027166_m1	DNA methyltransferase 3 alpha
GAD1	Hs01065893_m1	Glutamate decarboxylase 1 (full length, multiple transcripts)
GAD1 (variant GAD67)	Hs01065886_m1	Glutamate decarboxylase 1 (truncated form GAD67)
GAD1 (variant GAD25)	Hs00247564_m1	Glutamate decarboxylase 1 (truncated form GAD25)
TET1	Hs00286756_m1	Tet methylcytosine dioxygenase 1
TET2	Hs00325999_m1	Tet methylcytosine dioxygenase 1
TET3	Hs00379125_m1	Tet methylcytosine dioxygenase 1
BDNF (broad spectrum-bs)	Hs02718934_s1	Brain derived neurotrophic factor (Taqman Best Coverage) BDNF transcript variants 1–11,12,13,14,17,16,18,x1
BDNF IX (variant 1)	Hs04186202_s1	Brain derived neurotrophic factor BDNF, transcript variant 1 (BDNFIX)
Glucocorticoid (NR3C1-best coverage- bc)	Hs00353740_m1	nuclear receptor subfamily 3 group C member 1 (Taqman Best Coverage) Transcript Variants 1,2,3,4,5,6,7,8,x1,x2,x3, x5,x6,x7
Glucocorticoid (NR3C1)-(custom, cus)	AIY90ZY custom	Nuclear receptor subfamily 3 group C member 1 (NR3C1)-based on primer sequence: F: 5′-CAGCTCCTCAACAGCAACAACA-3′ R: 5′-GTGCTGTCCTTCCACTGCTCT-3 Transcript Variants 1,2,3,4,5,6, x5,x6,x7
IMPA2	Hs00274110_m1	Inositol monophosphatase 2
APBB2	Hs00921383_m1	Amyloid beta precursor protein binding family B member 2
CPT1A	Hs00912671_m1	Carnitine palmitoyltransferase 1A
APOBEC3A	AICXUP	Apolipoprotein B mRNA editing enzyme catalytic subunit 3A
CCR1	Hs00928897_s1	C-C motif chemokine receptor 1
FPRL2	Hs00266666_s1	Formyl peptide receptor 3
CNTNAP2	Hs04975510_cn	Contactin associated protein-like 2
CD4	Hs01058407_m1	CD4 molecule

Some of the duplicate or custom-made probes - DNMT1 (cus), (NR3C1-cus)-were chosen so sequences would more closely resemble the primer sequences used in our previous published results (Auta et al., 2013) which used a different method than the TaqMan probes utilized in this report. The differing portions of the gene covered in the original and these duplicate TaqMan probes for the same main gene are further specified in the information under the Gene Name column in the table. The GAD1 full length TaqMan probe contains the transcripts for the variants GAD67, GAD25, and multiple other transcripts.

2.3. RNA extraction and gene expression assay

RNA was isolated from blood lymphocyte samples and measures of gene expression assayed for genes of interest. Lymphocyte collection and qPCR assays are described fully in our previous publication (Sershen et al., 2021). The subject's blood was collected in ~4 × 10 ml EDTA tubes, put in an ice bucket, and rapidly processed. Lymphocytes (peripheral blood lymphocytes (PBL)) were extracted by Ficoll gradient procedures and pellets frozen as described previously. RNA was extracted from lymphocyte pellets with a TRIzol procedure. First strand cDNA was prepared using the Invitrogen SuperScript VILO cDNA Synthesis kit; up to 2.5 μg RNA measured with NanoDrop Lite (Thermo Scientific) was reacted with reagent mix, incubated at 42 °C for 60 min, and terminated at 85 °C for 5 min. The samples were frozen (−80 °C) until assayed. For qPCR, TaqMan Universal PCR Master Mix was used for

Table 3-
Correlations between MATRICS cognitive score and mRNA levels.

mRNA	Type of MATRICS domain score or overall composite score									
	Speed of processing		Attention-vigilance		Working memory		Visual learning		Overall composite	
	Schizophrenia	Controls	Schizophrenia	Controls	Schizophrenia	Controls	Schizophrenia	Controls	Schizophrenia	Controls
DNMT1 (or) (lg)	−0.337	−0.268	**−0.393***	−0.101	−0.355	−0.017	−0.289	−0.140	−0.346	−0.233
DNMT1 (cus)	−0.250	+0.002	**−0.349***	+0.116	***−0.251 D***	***+0.337 D***	***−0.283 D***	***+0.595***[B] D***	*−0.309 D*	*+0.236 D*
DNMT3A	**−0.228***	+0.077	**−0.396***	+0.018	−0.294	+0.080	***−0.361* D***	***+0.193 D***	−0.312	+0.066
GAD1(lg)	−0.035	−0.270	−0.135	−0.165	−0.216	−0.134	**−0.344***	−0.243	−0.264	−0.275
GAD67	−0.140	−0.321	−0.185	−0.231	−0.281	−0.070	−0.289	−0.060	**−0.361***	−0.232
BDNF (bc) (lg)	***−0.237 D***	***+0.341 D***	***−0.329 D***	***+0.226 D***	***−0.286 D***	***+0.361 D***	−0.221	+0.268	***−0.304 D***	***+0.432* D***
NR3C1 (bc) (sr)	−0.037	−0.128	+0.072	−0.025	−0.007	+0.158	−0.344*	+0.083	−0.120	+0.014
NR3C1 (cus)	−0.303	−0.041	**−0.362***	−0.113	−0.202	+0.063	***−0.371* D***	***+0.348 D***	**−0.364***	−0.003
TET2	−0.191	+0.017	−0.050	+0.061	−0.060	+0.206	−0.331*	−0.310	−0.194	+0.095
FPRF3 (lg)	−0.147	+0.289	−0.156	−0.187	−0.163	+0.119	**−0.377***	−0.099	***−0.306 D***	***+0.201 D***
CNTNAP2 (lg)	−0.254	−0.038	**−0.359***	−0.057	**−0.368***	+0.036	**−0.395***	+0.021	***−0.442** D***	***+0.035 D***

Each number represents Pearson (r) or for GAD67 Spearman (rho) correlation coefficient. N's– All subjects = $N = 57–69$, Schizophrenia $N = 27–37$, Controls $N = 29–32$. Statistical Significance: $*P < .05$, $**P < .01$, $***P < .001$. D = for the same MATRICS domain in the same row correlations are significantly different between schizophrenics and controls ($\alpha = 0.05$). [B] = correlations remain significant at BH corrected significant level ($\alpha = 0.05$) controlled for 8 MATRICS scores.

target amplification using the cDNA template and using primer/probes from the TaqMan Gene Expression Assay mix (see Table 2 for probes). Samples were assayed in triplicate, normalized against β-actin as the housekeeping gene, and ddCt = 2^(−dt) values calculated.

2.4. Statistical analysis

Data were analyzed using SPSS 25 and SAS 9.4. Statistical significance was set at $P < .05$, 2-tailed and trend level at $P < .10$. Correlation analysis (Pearson R or Spearman Rho) was used to examine the relationship between mRNA levels in lymphocytes and cognitive variables. The significance of difference in correlations was assessed using a SAS program (Weaver and Wuensch, 2013). Multiple regression analysis with interaction terms (age * group) was used to explore whether age moderates the relationship between mRNAs and MATRICS variables across schizophrenia and control groups (see supplement for statistical details).

3. Results

Table 1 presents the background characteristics of CSZ and controls. The CSZ patients were all treated with antipsychotics (34 % with clozapine), had substantial cognitive defects as indicated on MATRICS scores, and had long-term hospitalization and/or outpatient treatment, although we could not obtain accurate dates on length of illness from chart records. The CSZ were significantly older (mean 46 years) than the control sample (mean 36 years), and as expected from multiple previous studies had higher rates of cigarette smoking which may be related to a biological characteristic of the illness.

Patients with schizophrenia had mostly negative correlations between mRNA levels and MATRICS domain or overall composite scores, many of which were statistically significant; controls had either positive correlations or no statistically significant correlations between mRNA and MATRICS variables for many of the mRNAs (Table 3, supplementary Tables S1 and S2). There were significant differences in the correlations between CSZ and controls for some mRNAs with either overall composite score, and/or domain scores of visual learning, speed of processing, or attention-vigilance (Table 3, Fig. 1). The age difference between CSZ and controls did not explain or moderate the relationship between mRNA and MATRICS variables. The multiple regression analysis did not find any significant age*group effects for these associations for any of the correlations where there was a significant difference between CSZ and controls.

There were a few significant correlations between selected mRNA levels and PANSS symptom measures. There were no statistically significant correlations between any of the mRNA measures and hallucinations as assessed by the score on the P3 item of the PANSS. However, there were a few significant positive correlations of PANSS total positive symptom score and mRNA levels. There was a statistically significant correlation of FPRL2 mRNA, formyl peptide receptor 3, with PANSS Positive Symptom Total score ($r = +0.520$ $P = .002$) but this was not due to correlation with the hallucinations item in that scale. There was also a significant positive correlation between PANSS Positive symptom total score and TET2 mRNA ($r = +0.418$ $P = .02$), and also a modified version of the glucocorticoid receptor (NR3C1 -cus) ($r = +0.448$ $P = .005$).

4. Discussion

The present results showed significant negative correlations between mRNAs in lymphocytes measured in this study related to schizophrenia and cognitive deficits in these patients assessed by MATRICS battery. Higher levels of the mRNA were associated with poorer cognitive function. We cannot definitely determine whether these negative correlations represent a causative relationship. There is little previous data on peripheral markers of these mRNAs and cognitive function in schizophrenia; some studies have found a positive relationship of BDNF levels and cognitive function in schizophrenia (see below).

Our study also showed some significant differences in the relationship between the DNMT's, BDNF, FPRL3, and CNTNAP2 mRNAs and cognitive function in patients with schizophrenia compared to controls. Patient with schizophrenia showed a consistently negative correlation which was not found in controls. The differences between CSZ and controls were more frequent for the domain score of visual learning and the overall composite score. We have previously reported increases in DNMT mRNAs in the brains and lymphocytes of patients with schizophrenia compared to controls (Sershen et al., 2021). In the brain DNMT's may increase methylation of GABAergic neurons, which down regulates their inhibitory function. This could potentially be relevant to the differences in correlations between patients with schizophrenia vs controls reported in the present study. In this study the mRNAs more directly related to GABA, GAD1 and GAD67, did not show a difference between CSZ and controls, with both groups having negative correlations with the MATRICS variables. However, these GABAergic mRNAs in lymphocytes may not represent the same processes related to DNMTs as in brain function. The substantive interpretation of these differences in correlations between patients with schizophrenia and controls needs

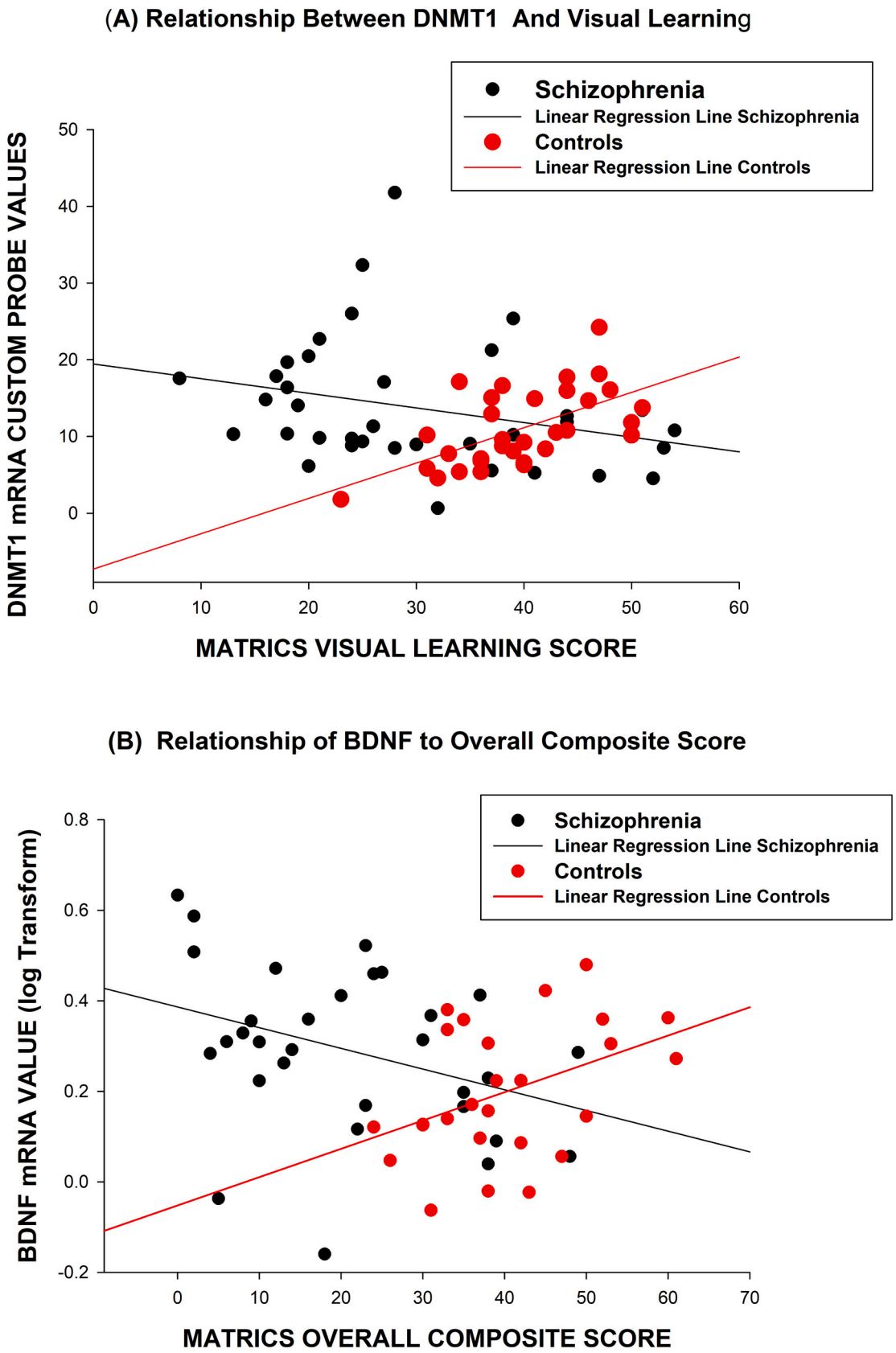


Fig. 1. Graphical representation of relationship between selected mRNAs and MATRICS variables.
See Table 3 for the exact correlations for these scatter plots for schizophrenia and control subjects.

further exploration.

There have been several previous studies investigating the relations of mRNA or plasma levels of their proteins in peripheral blood to cognitive measures in patients with schizophrenia or controls. Several studies and meta-analyses have found small but statistically significant ($P < .05$) positive correlations between peripheral blood levels of BDNF and cognitive scores in inpatients with schizophrenia using the MATRICS battery or other cognitive tests (Ahmed et al., 2015; Bora, 2019; Nieto et al., 2021; Nieto et al., 2023; Yang et al., 2019). In one study of drug-naïve or minimal antipsychotic treated patients with first-episode schizophrenia, Pan and associates(Pan et al., 2021) demonstrated that low mRNA and low protein BDNF in whole blood was associated with poorer performance on the MATRICS battery; higher levels of BDNF protein associated with better cognitive performance; essentially a positive correlation between BDNF levels and cognition. However, in this study we found consistently negative correlations with BDNF mRNA with cognitive function in schizophrenia which differed from the positive correlations in controls (as shown in Table 3). However, several previous studies had reported lower BDNF levels in schizophrenia whereas our own research (Sershen et al., 2021) found no significant differences in BDNF levels in patients with chronic schizophrenia compared to controls. Chase and associates found significant negative correlations between cannabinoid receptor mRNAs in peripheral lymphocytes and several cognitive measures from the MATRICS battery (Chase et al., 2016). Other studies have found a correlation with peripheral measured mRNAs and isolated cognitive function measures in schizophrenia– positive correlation of BCL-2 mRNA and working memory (Gou et al., 2021); positive correlation of a genetic variant of NR4A2 levels and auditory working memory (Ruiz-Sánchez et al., 2021); negative correlations with CRP and IL-1B with language test scores (Murphy et al., 2022); negative correlation to TFG-1 levels with visual learning and memory (Pan et al., 2022); and positive correlation of CSMD1 mRNA with working memory (Hatzimanolis et al., 2022).

We found a negative correlation of FPRL2 with the MATRICS battery scores, particularly verbal learning and overall composite; FPRL is associated with inflammatory response (Trojan et al., 2020; Tylek et al., 2021) but its role in pathology of schizophrenia is not established. We found that high levels of CNTNAP2 are consistently associated with cognitive deficits in schizophrenia. There is some evidence that CNTNAP2 is associated with cognitive impairment (Zhu et al., 2017) but its role in the pathology of schizophrenia is controversial (Ji et al., 2013; Toma et al., 2018). The pathophysiology of the cognitive deficits in schizophrenia may not be identical with the pathophysiology of other symptoms of schizophrenia. Therefore, it is important to investigate the molecular biology of the cognitive deficits of schizophrenia itself.

4.1. Limitations

Because the number of subjects assayed for each mRNA was not uniform for all the different mRNAs studied, the small differences in the number of subjects for each correlation (see supplement for exact numbers) could affect the reliability or interpretation of the correlations between different mRNAs. A larger sample size of schizophrenia and control subjects also could have provided stronger reliability for the correlations. We are uncertain about the potential influences of antipsychotic drugs on these correlations and there were too diverse antipsychotic drug treatments in the sample to do specific further analyses. We also do not know whether the biochemical relations found with mRNA in lymphocytes also reflects similar relationships from brain measures.

5. Conclusions

In patients with schizophrenia there were consistently negative correlations between mRNA we measured in lymphocytes and cognitive function assessed by MATRICS battery. Whether any of these represent a causative relation is uncertain. Correlations between mRNA levels in lymphocytes and MATRICS cognitive scores showed a different pattern in patients with schizophrenia vs non-psychotic controls.

Funding

This research was supported in part by NIH grant 1R01MH101043, A.G. PI, and a philanthropic grant to Dr. Smith's section at NKI.

CRediT authorship contribution statement

Robert C. Smith: Writing – review & editing, Writing – original draft, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Henry Sershen:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **AnMei Chen:** Writing – review & editing, Methodology. **Hua Jin:** Writing – review & editing, Conceptualization. **Alexandro Guidotti:** Funding acquisition, Conceptualization. **John M. Davis:** Writing – review & editing, Resources, Conceptualization.

Declaration of competing interest

The authors report no conflicts of interest potentially related to the research reported in this paper.

Data availability

Data on which this report is based is available on appropriate request in SPSS files from the principal author robert.smith@nki.rfmh.org.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scog.2024.100321.

References

Ahmed, A.O., Mantini, A.M., Fridberg, D.J., Buckley, P.F., 2015. Brain-derived neurotrophic factor (BDNF) and neurocognitive deficits in people with schizophrenia: a meta-analysis. Psychiatry Res. 226 (1), 1–13.

Auta, J., Smith, R.C., Dong, E., Tueting, P., Sershen, H., Boules, S., Lajtha, A., Davis, J., Guidotti, A., 2013. DNA-methylation gene network dysregulation in peripheral blood lymphocytes of schizophrenia patients. Schiz. Res. 150, 312–318.

Bora, E., 2019. Peripheral inflammatory and neurotrophic biomarkers of cognitive impairment in schizophrenia: a meta-analysis. Psychol. Med. 49 (12), 1971–1979.

Bowie, C.R., Harvey, P.D., 2006. Cognitive deficits and functional outcome in schizophrenia. Neuropsychiatr. Dis. Treat. 2 (4), 531–536.

Chase, K.A., Feiner, B., Rosen, C., Gavin, D.P., Sharma, R.P., 2016. Characterization of peripheral cannabinoid receptor expression and clinical correlates in schizophrenia. Psychiatry Res. 245, 346–353.

Gou, M., Pan, S., Tong, J., Zhou, Y., Han, J., Xie, T., Yu, T., Feng, W., Li, Y., Chen, S., Cui, Y., Tian, B., Tan, M.D.S., Wang, Z., Luo, X., Li, C.R., Zhang, P., Huang, J., Hong, L.E., Tan, Y., Tian, L., 2021. Effects of microRNA-181b-5p on cognitive deficits in first-episode patients with schizophrenia: mediated by BCL-2. J. Psychiatr. Res. 136, 358–365.

Green, M., 1998. The Scope of Neurocognitive Deficits in Schizophrenia. Schizophrenia From a Neurocognitive Perspective. Allyn and Bacon, Needham Heights, MA, pp. 41–60.

Hatzimanolis, A., Foteli, S., Stefanatou, P., Ntigrintaki, A.A., Ralli, I., Kollias, K., Nikolaou, C., Gazouli, M., Stefanis, N.C., 2022. Deregulation of complement components C4A and CSMD1 peripheral expression in first-episode psychosis and links to cognitive ability. Eur. Arch. Psychiatry Clin. Neurosci. 272 (7), 1219–1228.

Ji, W., Li, T., Pan, Y., Tao, H., Ju, K., Wen, Z., Fu, Y., An, Z., Zhao, Q., Wang, T., He, L., Feng, G., Yi, Q., Shi, Y., 2013. CNTNAP2 is significantly associated with schizophrenia and major depression in the Han Chinese population. Psychiatry Res. 207 (3), 225–228.

Kay, S.R., Fizzbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Liu, Y., Wang, G., Jin, H., Lyu, H., Liu, Y., Guo, W., Shi, C., Meyers, J., Wang, J., Zhao, J., Wu, R., Smith, R.C., Davis, J.M., 2019. Cognitive deficits in subjects at risk for psychosis, first-episode and chronic schizophrenia patients. Psychiatry Res. 274, 235–242.

Murphy, C.E., Walker, A.K., O'Donnell, M., Galletly, C., Lloyd, A.R., Liu, D., Weickert, C. S., Weickert, T.W., 2022. Peripheral NF-κB dysregulation in people with

schizophrenia drives inflammation: putative anti-inflammatory functions of NF-κB kinases. Transl. Psychiatry 12 (1), 21.
Nieto, R.R., Carrasco, A., Corral, S., Castillo, R., Gaspar, P.A., Bustamante, M.L., Silva, H., 2021. BDNF as a biomarker of cognition in schizophrenia/psychosis: an updated review. Front. Psychol. 12, 662407.
Nieto, R.R., Silva, H., Armijo, A., Nachar, R., González, A., Castañeda, C.P., Montes, C., Kukuljan, M., 2023. BDNF and cognitive function in Chilean schizophrenic patients. Int. J. Mol. Sci. 24 (13).
Nuechterlein, K., Green, M., Kern, R., Baade, L., Barch, D., Cohen, J., Essock, S., Fenton, W., Frese, F., Gold, J., Goldberg, T., Heaton, R., Keefe, R., Kraemer, H., Seidman, L., Stover, E., Weinberger, D., Young, A., Zalcan, S., Mardder, S., 2008. The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity. Am. J. Psychiat. 165 (2), 203–213.
Pan, S., Feng, W., Li, Y., Huang, J., Chen, S., Cui, Y., Tian, B., Tan, S., Wang, Z., Yao, S., Chiappelli, J., Kochunov, P., Chen, S., Yang, F., Li, C.R., Tian, L., Tan, Y., Elliot Hong, L., 2021. The microRNA-195 - BDNF pathway and cognitive deficits in schizophrenia patients with minimal antipsychotic medication exposure. Transl. Psychiatry 11 (1), 117.
Pan, S., Zhou, Y., Yan, L., Xuan, F., Tong, J., Li, Y., Huang, J., Feng, W., Chen, S., Cui, Y., Yang, F., Tan, S., Wang, Z., Tian, B., Hong, L.E., Tan, Y.L., Tian, L., 2022. TGF-β1 is associated with deficits in cognition and cerebral cortical thickness in first-episode schizophrenia. J. Psychiatry Neurosci. 47 (2), E86–e98.
Ruiz-Sánchez, E., Jiménez-Genchi, J., Alcántara-Flores, Y.M., Castañeda-González, C.J., Aviña-Cervantes, C.L., Yescas, P., Del Socorro González-Valadez, M., Martínez-Rodríguez, N., Ríos-Ortiz, A., González-González, M., López-Navarro, M.E., Rojas, P., 2021. Working memory deficits in schizophrenia are associated with the rs34884856 variant and expression levels of the NR4A2 gene in a sample Mexican population: a case control study. BMC Psychiatry 21 (1), 86.
Sershen, H., Guidotti, A., Auta, J., Drnevich, J., Grayson, D.R., Veldic, M., Meyers, J., Youseff, M., Zhubi, A., Faurot, K., Wu, R., Zhao, J., Jin, H., Lajtha, A., Davis, J.M., Smith, R.C., 2021. Gene expression of methylation cycle and related genes in lymphocytes and brain of patients with schizophrenia and non-psychotic controls. Biomark. Neuropsychiatry 5.
Toma, C., Pierce, K.D., Shaw, A.D., Heath, A., Mitchell, P.B., Schofield, P.R., Fullerton, J. M., 2018. Comprehensive cross-disorder analyses of CNTNAP2 suggest it is unlikely to be a primary risk gene for psychiatric disorders. PLoS Genet. 14 (12), e1007535.
Trojan, E., Bryniarska, N., Leśkiewicz, M., Regulska, M., Chamera, K., Szuster-Głuszczak, M., Leopoldo, M., Lacivita, E., Basta-Kaim, A., 2020. The contribution of formyl peptide receptor dysfunction to the course of neuroinflammation: a potential role in the brain pathology. Curr. Neuropharmacol. 18 (3), 229–249.
Tylek, K., Trojan, E., Regulska, M., Lacivita, E., Leopoldo, M., Basta-Kaim, A., 2021. Formyl peptide receptor 2, as an important target for ligands triggering the inflammatory response regulation: a link to brain pathology. Pharmacol. Rep. 73 (4), 1004–1019.
Weaver, B., Wuensch, K.L., 2013. SPSS and SAS programs for comparing Pearson correlations and OLS regression coefficients. Behav. Res. Methods 45 (3), 880–895.
Yang, Y., Liu, Y., Wang, G., Hei, G., Wang, X., Li, R., Li, L., Wu, R., Zhao, J., 2019. Brain-derived neurotrophic factor is associated with cognitive impairments in first-episode and chronic schizophrenia. Psychiatry Res. 273, 528–536.
Zhu, B., Chen, C., Xue, G., Lei, X., Wang, Y., Li, J., Moyzis, R.K., Li, J., Dong, Q., Lin, C., 2017. Associations between the CNTNAP2 gene, dorsolateral prefrontal cortex, and cognitive performance on the Stroop task. Neuroscience 343, 21–29.