Evaluation of the association between serum proteins and neurocognitive performance in bipolar disorder and schizophrenia patients

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INTRODUCTION

Despite the fact that various research efforts over the past decades have yielded important insights into the pathophysiology of psychiatric disorders, clinically useful biomarkers have yet to be established in psychiatry. In this study, we analyzed the association of the serum levels of several proteins in patients with bipolar disorder (BP) or schizophrenia (SCZ) with several cognitive tests. Our overall goal was to discover potential circulating biomarkers related to neurocognitive performance and, secondarily, the role of protein quantitative trait loci (pQTL) in this interplay.

METHODS

113 schizophrenia and 125 bipolar patients belonging to the German KFO241/PsyCourse cohort (www.kfo241.de;) were included in this study. Analysis of a selected panel of 95 serum proteins (Table 1) was performed using a set of 155 antibodies in a high-throughput antibody-based assay. Log-transformation and standardization were done for median fluorescent intensities to consider in downstream analyses. Cognition tests in our study included Trail-Making-Test A & B, Verbal Digit Span Forward & Backward, Digit-Symbol, and Multiple-Choice Vocabulary Intelligence. Trail-Making-Test checks executive function, Verbal-Digit-Span test evaluates short-term and working memory, Digit-Symbol-Test assesses the psychomotor speed and Multiple-Choice Vocabulary Intelligence test investigates crystallized IQ. Age, sex, duration of illness and diagnosis were considered as covariates. Linear regression model in R program were applied to the association analysis between patient's cognition tests standardized results and the measured proteins levels.

The pQTL analyses were based on DNA samples of these patients that were genotyped (Infinium PsychArray) and underwent genotype imputation (1000 Genomes Phase 3 reference panel). Age, sex, duration of illness and diagnosis were used as covariates in the pQTL analyses using PLINK 1.9.

No.	Name	No.	Name	No.	Name	No.	Name	No.	Name
1	MIF	20	CCL5	39	CFP	58	HP	77	APOF
2	CD40LG	21	CEACAM5	40	IL15	59	CSF2	78	F7
3	C4BPA	22	FCN2	41	AXL	60	C4B	79	AGER
4	C8B	23	NRG1	42	APOD	61	IL1A	80	IL5
5	CFB	24	CCL11	43	IL12B	62	SERPING1	81	IL6
6	CFI	25	LTA	44	IL13	63	CFH	82	APOE
7	C1R	26	C1RL	45	IL7	64	APOB	83	CCL8
8	MBL2	27	ERBB4	46	IL4	65	TNF	84	C7
9	C1QA	28	VIP	47	CCL16	66	APOM	85	IL25
10	CSK	29	APOL1	48	C6	67	APOC1	86	ACE
11	IL6R	30	IL16	49	IL11	68	C4BPB	87	EGF
12	VWF	31	PTK2B	50	IGFBP2	69	IL17A	88	C9
13	VCAM1	32	C8A	51	BACE1	70	CFD	89	FCN3
14	APOH	33	MASP2	52	IL1B	71	IFNG	90	AVP
15	A2M	34	CD40	53	C8G	72	XCL2	91	APOA2
16	TNFRSF1B	35	LEP	54	C4A	73	CXCL8	92	APOC3
17	TNC	36	IL3	55	APOA1	74	KITLG	93	TNIK
18	ROCK2	37	IL1RAP	56	CCL18	75	APOC4	94	aAlbumin
19	PPBP	38	PPY	57	TGFB1	76	IL10	95	hIgG

Table1. List of 95 assayed serum proteins by antibody-based microarray in this study

	SCZ	BD
Subjects (n)	108	100
Sex (%female)	40.7 %	58%
Age	45 ± 14	46 ± 14
Duration of illness(years)	14.9	13.5
PANSS_Positive	12.8 ± 5.1	9.4 ± 2.9
PANSS_Negative	13.9 ± 6.1	10.5 ± 3.9
PANSS_General	26.6 ± 8.4	23.6 ± 6.5
YMRS	2.4 ± 4.3	4.2 ± 5.9
BDI_II	11.4 ± 10.7	12.6 ± 12.2
IDSC	14.4 ± 9.7	14.1 ± 11.2

Table2. Demographic and psychopathological data of the patients

RESULTS

After data cleaning, applying log-transformation and standardization and removing outliers, 208 cases remained. Demographic and psychopathological data of these 208 patients is presented in Table 2. The results of our study showed a nominal (P<0.05) association of 37 proteins with Trail-Making-Test part A (Inverse relation) (i.e. IL1A [p-value=0.0010], IL3 [p_value= 0.0010], ROCK2 [p-value= 0.0041]). Furthermore, 18 proteins were detected to be associated with Digit-Symbol-Test (Direct relation) with a p-value<0.05 (i.e. TNIK [p-value=0.0036], XCL2 [p-value=0.0037], KITLG [p-value=0.0098]) (Figure 1). For Tail-Making-Test part B and Verbal Digit Span Backward, just one associated protein with a p-value<0.05 was found (C9 [p-value=0.0446] and APOH [p-value=0.0469] respectively). No significant association of protein levels was observed with Verbal Digit Span Forward and Multiple-Choice Vocabulary Intelligence tests.It should be noted that none of the measured protein parameters remained significant after Bonferroni adjustment. The pQTL analysis in our sample did not yield any significant effect.

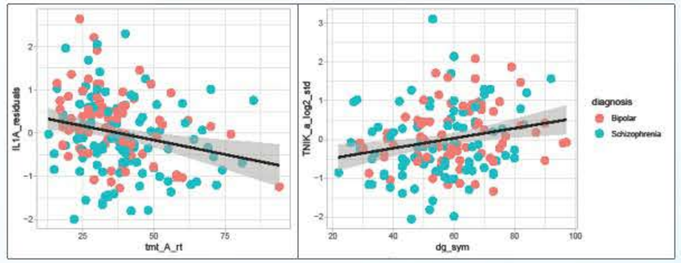

Figure 1. Scatter plots and linear regression lines between tmt_A_rt test and IL1A serum Level (Left) and dg_sym test and TNIK serum Level (Right)

DISCUSSION

An overview of identified significant proteins nominally associated with both Trail-Making-Test part A and Digit-Symbol-Test, reveals that the majority of them are directly or indirectly involved in the immune system, especially inflammation, as numerous previous evidence have mentioned regarding inflammatory processes in BD and SCZ. As an example, IL1, IL3 and IL6R are three well-known inflammatory proteins of shared between Trail-Making-Test part A and Digit-Symbol-Test that measure executive function and psychomotor speed, respectively. Taken together, although none of the individual protein parameters remains significant after Bonferroni correction, our primary findings suggest that inflammatory cytokines as a group are somehow related with these cognitive domains. These results need be replicated in large sample size investigations. The limitations of our study include a relatively modest sample size, and also, medication or daily fluctuation effects were not considered in these preliminary analyses (Ongoing work in our group). Overall, the preliminary results of this pilot study indicate the role of inflammation in the neurocognitive function of SCZ and BD patients and suggest the potential of the related involved cytokines as plausible biomarkers for cognitive performance in SCZ and BD.

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