Psychiatry Research 271 (2019) 111–113

Contents lists available at ScienceDirect

Psychiatry Research

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

Short communication

Traumatic experiences and cognitive profiles of schizophrenia cases influenced by the BDNF Val66met polymorphism

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ARTICLE INFO

Keywords:
BDNF
Trauma
Schizophrenia

ABSTRACT

The association of early trauma exposure with current cognition was examined in a research series of 56 schizophrenia cases with respect to the BDNF Val66Met polymorphism (rs6265, Val66Val, Val66Met, Met66Met), as met allele carriers have reduced neurotrophic activity. The Perceptual Organization Index had a significant negative correlation with trauma exposures only in met carriers, including early physical abuse, general trauma after age 18 years, and physical abuse. Within the Val66Val subgroup, there were no significant correlations between WAIS indices and traumatic experiences.

1. Introduction

We previously demonstrated that emotional trauma was significantly related to the severity of general psychopathology symptoms in schizophrenia cases harboring the methionine (Met) allele of brain-derived neurotrophic factor (BDNF) Val66Met polymorphism (Veras et al., 2018). The Met allele decreases BDNF release probability (Jing et al., 2016), producing lower efficiency in neurotrophic activity, which is required for neurogenesis and neuroplasticity (Pattwell et al., 2012). It is associated with impaired episodic memory and lesser hippocampal activation (Aas et al., 2013). Met carriers with schizophrenia spectrum or bipolar disorders exposed to childhood sexual abuse evidence reduced grey matter volumes, consistent with the reduced BDNF mRNA levels in Met carriers who were exposed to childhood sexual abuse (Aas et al., 2013).

As a next step to these studies, the current analysis considered the relationship between early trauma and cognition in a richly characterized sample of schizophrenia research cases that included BDNF heterozygous for Val66Met polymorphism and Val66Val BDNF cases.

2. Methods

The study participants included 20 healthy comparison subjects and 56 cases with DSM 5 schizophrenia or schizoaffective disorder; age 18–55 years of age, who were recruited from treatment settings at a large urban public hospital. The Institutional Review Board approved the study and all subjects provided written informed consent. The cases were clinically stable with no medication changes for at least one month. Diagnoses were determined with the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994) (DIGS). Cognition was assessed with the Wechsler Adult Intelligence Scale, 3rd Edition (Wechsler, 1997) (WAIS-III) and indices were calculated for Perceptual Organization, Working Memory and Processing Speed and Verbal

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https://doi.org/10.1016/j.psychres.2018.11.029
Received 18 March 2018; Received in revised form 14 November 2018; Accepted 14 November 2018
Available online 15 November 2018
0165-1781/

Comprehension. Symptom assessments included the Positive and Negative Syndrome Scale (Kay et al., 1987) (PANSS), summarized as positive, negative and general psychopathology scores, Hamilton Depression (Hamilton, 1960) (HAM-D) and Anxiety (Hamilton, 1959) (HAM-A) scales and the Young Mania Rating Scale (Young et al., 1978). Early trauma exposure and trauma exposures after age 18 years were assessed with the Early Trauma Inventory (Bremner et al., 2000) (ETI).

Genomic DNA was isolated from whole blood samples using the QIAamp DNA blood kit (Qiagen) according to the manufacturer's standard protocol. DNA samples were genotyped at BDNF Val66Met (rs6265) using a commercially available Taqman 5′ exonuclease assay (ABI).

ANCOVA and *t*-test examined the continuous measures and Chi-square was used for categorical variables. Pearson's correlation coefficients examined the associations between the ETI scales and WAIS-III subscales and indices with Alpha for significance was set at $p < 0.05$. Cases were stratified by BDNF gene variants (Val66Met or Met66Met; Val66Val BDNF polymorphism groups). Comparisons between correlation coefficients were proceeded by Fisher`s *r* to *Z* tests.

3. Results

Cases and control groups were similar in age (42.2 ± 9.8 versus 36.9 ± 8.2: $p > 0.050$), educational attainment (12.5 ± 2.7 versus 15.0 ± 2.1: $p > 0.050$); proportion unmarried (69.6% versus 55.5%: $p > 0.050$), sex (64.2% versus 55.0% male: $p > 0.050$) and ethnicity (28 African-ancestry, 13 white, 12 Asian versus 12 African-ancestry, 2 white, 6 Asian).

Although Met allele frequency was slightly lower in cases (15/112 – 13.3%) than controls (7/40 – 17.5%), this result was not statistically different for these groups nor between the ethnic groups. Cases reported significantly higher levels of emotional abuse ($p = 0.002$) and general trauma exposure both before ($p = 0.009$) and after age 18 years ($p = 0.004$), compared to controls. All measures of WAIS indices proved to be lower in cases ($p < 0.001$) than control and there were no significant interactions for group and sex. Subgroups of cases with the two different BDNF Val66Met genotypes (Val66Met or Met66Met) were similar in age, all symptoms and trauma exposures. Sex specific analyses in Met cases showed significantly more emotional abuse in female than male cases (6.0 ± 6.6 vs. 23.0 ± 12.7, $p = 0.004$), but showed males had more severe negative symptoms (15.7 ± 5.6 vs. 10.3 ± 3.5, $p = 0.024$) and general psychopathology (31.8 ± 7.6 vs. 24.6 ± 4.7, $p = 0.049$). There were no sex differences in the Val group.

Correlations between ETI scores and cognitive measures in the subgroups and comparisons between the groups are shown in Table 1. The Perceptual Organization Index, which measures nonverbal reasoning, visual-motor integration, was negatively correlated with early physical abuse ($r = -0.619$ $p = 0.018$), and general trauma after age 18 years ($r = -0.682$ $p = 0.007$) in the Met carrier sample only. Notably, all these traumatic experiences were related with perceptual organization. The relationship between physical abuse and perceptual organization was significantly greater among Met allele carriers than Val cases ($r = -0.666$, $p = 0.009$ vs $r = -0.084$, $p = 0.630$: Fisher's *Z* test, $p = 0.020$).

There was a strong negative correlation between Full Scale IQ scores and the ETI General Events scores ($r = -0.586$ $p = 0.028$) after age 18 years in the Met allele carriers only. Likewise, the Perceptual Organization Index was negatively correlated with general trauma after age 18 years ($r = -0.682$ $p = 0.007$) in the Met allele carriers only. Within the Val66Val subgroup ($N = 35$), there were no significant correlations between WAIS indices and traumatic experiences.

4. Discussion

Early trauma and trauma after age 18 years were significantly associated with the degree of cognitive impairment in the schizophrenia

Table 1
Early Trauma and WAIS III IQ and Indices:
Comparisons of correlations between Met variant carriers and the Val66Val BDNF sample.

Early traumameasures:	Verbal IQ*r (N) P*	Performance IQ*r (N) P*	Full scale IQ*r (N) P*	Verbal comprehension*r (N) P*	Perceptual organization*r (N) P*	Working memory*r (N) P*	Processing speed*r (N) P*
General Events							
Met variants	−0.199 (14) 0.496	−0.512(14) 0.061	−0.463 (14) 0.096	−0.447 (14) 0.109	**−0.537 (14) 0.048**	−0.288 (14) 0.319	−0.326 (14) 0.255
Val66val	−0.234 (35) 0.176	−0.252(35) 0.144	−0.261 (35) 0.130	−0.247 (35) 0.153	−0.298 (35) 0.082	−0.162 (35) 0.352	−0.069 (35) 0.694
Fisher`s *Z* test	*P* = 0.458	*P* = 0.189	*P* = 0.252	*P* = 0.256	*P* = 0.201	*P* = 0.352	*P* = 0.221
Emotional Abuse							
Met variants	−0.059 (14) 0.841	−0.114 (14)0.698	−0.182 (14) 0.534	−0.123 (14) 0.675	−0.230 (14) 0.430	−0.208 (14) 0.475	−0.028 (14) 0.926
Val66val	−0.069 (35) 0.694	−0.240 (35)0.165	−0.152 (35) 0.384	−0.023 (35) 0.895	−0.179 (35) 0.305	−0.165 (35) 0.344	−0.107 (35) 0.541
Fisher`s *Z* test	*P* = 0.489	*P* = 0.355	*P* = 0.465	*P* = 0.387	*P* = 0.439	*P* = 0.449	*P* = 0.410
Sexual Abuse							
Met variants	0.050 (14) 0.864	−0.359 (14)0.208	−0.161 (14) 0.582	−0.083 (14) 0.777	−0.282 (14) 0.329	0.128 (14) 0.663	−0.267 (14) 0.356
Val66val	−0.125 (35) 0.476	−0.167 (35)0.338	−0.155 (35) 0.375	−0.145 (35) 0.406	−0.159 (35) 0.362	−0.087 (35) 0.620	−0.100 (35) 0.567
Fisher`s *Z* test	*P* = 0.414	*P* = 0.277	*P* = 0.493	*P* = 0.429	*P* = 0.356	*P* = 0.268	*P* = 0.310
Physical Abuse							
Met variants	−0.203 (14) 0.486	**−0.619 (14)0.018**	−0.525 (14) 0.054	−0.458 (14) 0.099	**−0.666 (14) 0.009**	−0.343 (14) 0.231	−0.405 (14) 0.151
Val66val	−0.227 (35) 0.189	−0.162 (35)0.352	−0.215 (35) 0.214	−0.231(35) 0.183	−0.084 (35) 0.630	−0.236 (35) 0.172	−0.084 (35) 0.632
Fisher`s *Z* test	*P* = 0.471	*P* = 0.055	*P* = 0.148	*P* = 0.229	***P* = 0.020**	*P* = 0.369	*P* = 0.162
General Events post 18 years-old							
Met variants	−0.356 (14) 0.212	**−0.682 (14)0.007**	**−0.586(14) 0.028**	**−0.540 (14) 0.046**	**−0.616 (14) 0.019**	−0.389 (14) 0.169	**−0.585 (14) 0.028**
Val66val	−0.104 (35) 0.553	−0.069 (35)0.695	−0.093 (35) 0.594	−0.146 (35) 0.404	−0.145 (35) 0.407	−0.015 (35) 0.932	0.289 (35) 0.092
Fisher`s *Z* test	*P* = 0.222	***P* = 0.014**	***P* = 0.049**	*P* = 0.095	*P* = 0.051	*P* = 0.129	*P* = 0.143

cases who carry the Met allele of the BDNF Val66Met polymorphism, although not in other schizophrenia cases. This finding suggests an etiological role for trauma for cognitive impairment in the schizophrenia cases harboring a Met allele in BDNF. The Val66Val BDNF group examined was larger in size, yet no association between trauma and cognition was show within this group. Schizophrenia is etiologically heterogeneous and larger studies can elucidate if trauma related schizophrenia is more frequent among Met allele carriers. Certainly other genetic variation and exposures, perhaps even intergenerational ones, are also relevant to the pathophysiology that produces the final common syndrome of schizophrenia. Specifically, the mean symptoms and cognitive test scores were similar for the two BDNF Val66Met subgroups, consistent with the etiological heterogeneity. Deeper analyses of the data were not possible, as the trauma measures were highly inter-correlated.

Full Scale IQ scores in the Met allele carriers was robustly diminished in accord with general trauma severity and physical abuse in childhood, as well as trauma exposure after age 18 years. The impact of early trauma on the WAIS Perceptual Organization Index includes deficits in nonverbal fluid reasoning, visual-motor integration, and visual-spatial problems that are so crucial to real life function. Decreased brain activity in schizophrenia for the regulation of attention, encoding of visual information, perceptual decision-making and response generation is consistent with these deficits (Silverstein et al., 2010) and supports the central importance of disrupted perceptual organization in the underpinnings of the disease.

Early life stress exposure is a negative regulator of BDNF and glucocorticoid receptors (GR) expression in the hippocampus, in the long term, favoring the vulnerability to develop neuropsychiatric disorders, especially upon additional stress exposures (Daskalakis et al., 2015). An alternative consideration is whether reduced neural capacity leads to a compensatory brain activation that might produce or activate trauma memories. A study of spatial working memory monitored by fMRI found that subjects with schizophrenia had to recruit more cortical regions for the task (Lee et al., 2008). In this same study, false memory errors were also associated with greater bilateral prefrontal activation. It is plausible that neural strategies to compensate for deficits of perceptual organization, working memory and visuospatial function may lead to a higher recognition of new stimuli as (false) memories. False trauma memory was more frequent among adolescents with posttraumatic stress disorder who experienced childhood sexual abuse (Goodman et al., 2011). In our sample this influence could be even heightened because of psychosis. These aspects have to be taken into consideration of our findings, as we collected early traumatic experiences retrospectively.

In addition to showing specific cognitive effect of trauma in BDNF Met carriers with schizophrenia, this work calls attention to the need to meaningfully investigate subgroups of cases under the umbrella of the schizophrenia syndrome. Further work is yet needed. This small preliminary study calls attention to studies that can examine causation with adequate power. Because of the hypothesis-based proof-of-concept nature of these analyses, correction for multiple testing was not applied. No other study had rigorous research assessments of early trauma exposures, cognition and demographics in extremely well-characterized cases and control subjects. All samples with schizophrenia related psychosis are heterogeneous. Exploring that complexity is a strength of this study. Although small in size in comparison to genetic research samples, this study contrasts a single nucleotide difference in a well-studied gene to evidence the possibility of a gene-environment interaction with a strong phenotype effect.

Acknowledgments

The present work was made with the support of CNPq, Conselho Nacional de Desenvolvimento Científico e Tecnológico, Brazil (150289/2017-0) and by NIH Grants RC1-MH088843 (DM), 5K24MH001699 (DM) and MH086651 (MVC).

The authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.11.029.

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