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ORIGINAL PAPER

Cognitive Impairment in Schizophrenia: Interplay of BDNF and Childhood Trauma? A Review of Literature

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Abstract Cognitive impairment is a core feature of schizophrenia. These deficits can also serve as an endophenotype for the illness in genetic studies. There is evidence that suggests that cognition can be considered a reasonable target for intervention in both schizophrenia and bipolar disorder. One of the most studied genetic phenotypes for psychosis is brain-derived neurotrophic factor (BDNF) Val66Met polymorphisms. BDNF has an established role in neuronal development and cell survival in response to stress and is abnormally expressed in schizophrenia. Studies have shown that childhood trauma is associated with poor prognosis of schizophrenic patients. BDNF-Val66Met polymorphism has been shown to moderate the impact of childhood adversity on later expression of affective symptoms, suggesting the possibility of gene environment interactions. Considering the recent advances of neuroscience an up to date review of relevant literature is warranted in this field. This article reviews the current literature available regarding associations between the Val66Met polymorphism, childhood trauma and cognitive dysfunction in schizophrenia.

Keywords BDNF · BDNFval66met polymorphism · Childhood trauma · Cognition in schizophrenia · Genetics · Endophenotype

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Introduction

Cognitive impairment is a core feature of schizophrenia [1–3]. Individuals with schizophrenia have a broad range of neurocognitive impairments, including abnormalities in attention, executive function, visual and verbal learning and memory, working memory, processing speed, and social cognition [4]. These impairments are major determinants of functional outcome in schizophrenia [4, 6]. Unfortunately, antipsychotic medications have minimal effects on cognition [5, 6]. This association between cognition and outcome is robust—it was replicated and extended in many countries, using many different types of assessments, in different patient groups across the phase of illness, including prodromal [7, 8]. Given the importance of cognition as a determinant of functional outcomes, and the minimal impact of antipsychotic medications on cognition and functional outcomes, studies of the cognitive impairment in schizophrenia have grown in recent decades.

Genetic and environmental factors have been recognized as playing an important role in the development of Schizophrenia, as well as with the cognitive impairment in the disorder [9, 10]. Cognitive deficits are clearly central to the illness and meet several critical criteria for being considered as important "endophenotypes" [11]. Linkage and association studies have paid increasing attention to neurocognition as a putative endophenotype [12]. They are stable, present in attenuated form in relatives, presumed to be genetically simpler than the illness phenotype, and measured with high reliability. In addition, they are among the most heritable of all illness-related traits, at least in families affected by severe mental illness. The heritability of a variety of cognitive functions in families of people with schizophrenia has been demonstrated in a multiple studies [13].

Considerable evidence now indicates that environmental factors have a causative role in schizophrenia. Elevated incidence of the disease has been linked to a wide range of disturbances in the prenatal environment and to social factors and drug intake during adolescence [13]. More recently, researchers have attempted to investigate the interactions between genetic and environmental factors in the development of numerous clinical disorders, including schizophrenia. So far multiple genes and environmental factors have been implicated for cognitive impairment associated with schizophrenia, but in this review we focus on BDNFval66met polymorphism, childhood trauma and their influence on cognition by affecting the amygdala-hippocampal area that is associated with regulation of emotion and cognition.

Methods

All major databases were searched using the keywords: BDNF, BDNFval66met polymorphism, childhood trauma, schizophrenia and cognition in schizophrenia. Peer-reviewed papers published in English from 2005 to 2015 were identified. Reference lists provided by the initially identified articles provided additional articles for this review. We selected articles based on the following criteria:

(1) Published in a peer-reviewed journal.
(2) Reporting a relationship between BDNFval66met polymorphism or BDNF levels, childhood trauma and cognition.

A total of nine articles (see Table 1) were found using the search engine. Out of these, only one article studied a relationship between BDNFval66met polymorphism, childhood

Table 1 List of studies

Author	Title	Selected for review or not?
Bortoluzzi et al. [44]	Mineralocorticoid receptor genotype moderates the association between physical neglect and serum BDNF	No
Theleritis et al. [43]	Brain derived Neurotropic Factor (BDNF) is associated with childhood abuse but not cognitive domains in first episode psychosis	Yes
Hernaus et al. [45]	Brain-derived neurotrophic factor/FK506-binding protein 5 genotype by childhood trauma interactions do not impact on hippocampal volume and cognitive performance	No
Vrijsen et al. [46]	Association between genes, stressful childhood events and processing bias in depression vulnerable individuals	No
Aas et al. [42]	BDNF val66met modulates the association between childhood trauma, cognitive and brain abnormalities in psychoses	Yes
Savitz et al. [47]	Genotype and childhood sexual trauma moderate neurocognitive performance: a possible role for brain-derived neurotrophic factor and apolipoprotein E variants	No
Roth et al. [48]	Lasting epigenetic influence of early-life adversity on the BDNF gene	No
Dalvie et al. [40]	The BDNF p.Val66Met polymorphism, childhood trauma, and brain volumes in adolescents with alcohol abuse	No
Alemany et al. [49]	Childhood abuse, the BDNF-Val66Met polymorphism and adult psychotic-like experiences	No

trauma and cognition, while one other article studied the relationship between BDNF levels, childhood trauma and cognition.

Results and Discussion

Cognition

Neurocognitive deficits have long been acknowledged as a core feature in schizophrenia. Emil Kraepelin differentiated dementia praecox (schizophrenia) from manic-depressive psychosis (bipolar disorder) in the early 20th century, believing that patients with bipolar disorder exhibited affective and cognitive symptom-free, euthymic intervals between mood episodes [14]. Traditional approaches to the study of cognition emphasize an information-processing view that has generally excluded emotion. In contrast, the recent emergence of cognitive neuroscience as an inspiration for understanding human cognition has highlighted its interaction with emotion [15]. Cognitive neuroscience data indicate that emotion and cognition, as well as their underlying neural networks, are in fact in close interaction. First, it turns out that emotion can serve cognition, as exemplified by its critical contribution to decision-making or to the enhancement of episodic memory. Second, it is also observed that reciprocally cognitive processes such as reasoning, conscious appraisal or explicit representation of events, can modulate emotional responses like promoting or reducing fear [16]. Third, neurobiological data indicate that reciprocal amygdalar-hippocampal influences underlie such mutual regulation of emotion and cognition [17]. Prefrontal cortex has been usually associated with negative findings of schizophrenia and much research has been conducted to elucidate its role in cognitive decline. Although there

is some evidence of prefrontal cortex being involved, [18] neuro-psychological and anatomical findings do not explicitly support this assumption [19]. In search of the link between cognitive decline in schizophrenia and human brain, recent studies have shifted focus to the amygdalar-hippocampal area.

Brain-Derived Neurotrophic Factor (BDNF)

BDNF is a widely investigated marker in neuropsychiatric disorders and may be important in the pathophysiology of schizophrenia [20, 21]. BDNF protein is involved in neurogenesis and neuroplasticity in the brain. BDNF concentrations can be measured in serum, plasma or whole blood. These concentrations are highly correlated with those in cerebrospinal fluid, as BDNF crosses the blood–brain barrier [22]. Several meta-analyses have shown that there may be a correlation between low BDNF levels and the emergence of schizophrenia [23]. Taking this a step further, researchers focused on the single nucleotide polymorphism (SNP) Val66Met, also known as G189A or rs6265. It represents substitution of a valine (Val) by a methionine (Met) at codon 66. This substitution in the pro-region of BDNF modifies sorting of the protein and its availability in the synaptic cleft [24]. This polymorphism is relatively common (65 % Val66Val to 35 % Val66Met in the Caucasian population), making any functional consequence potentially significant [25]. Schizophrenia is associated with structural and functional abnormalities of the hippocampus, which have been suggested to play an important role in the formation and emergence of schizophrenia syndrome [26, 27]. In terms of structural abnormalities, several magnetic resonance imaging studies and meta-analyses of the relevant studies have shown significant bilateral hippocampal volume reduction [28, 29]. BDNF is highly expressed in the hippocampus and is associated with neuronal activation and remodeling of this brain region [30, 31].

Childhood Trauma

Childhood trauma is prevalent in patients with psychosis and severely affects disease course and outcome [32–35]. Patients with FEP (first episode psychosis) who have experienced CT (childhood trauma) present with worse cognitive performances compared with patients who did not have such early adverse experiences [36, 37]. These cognitive deficits may be associated with abnormalities in hippocampal and amygdala volume [38]. Healthy individuals who are Met carriers for the BDNF Val/Met polymorphism and have been exposed to early life stress show smaller amygdala and hippocampal volume associated with a decline in working memory [39].

GxE Interaction

Although there has been some research investigating the relationship between BDNF-val66Met polymorphism, childhood trauma and brain volumes, the evidence is not conclusive. Some studies show no correlation [40] and some show good correlation [41] between some of these factors. Not many studies exploring the interaction between all three of these have been reported. From our search there was only one report by Aas et al. [42] that studied the correlation between these three factors and one by Theleritis et al. [43] that examined BDNF levels (not BDNFval66met polymorphism) and its relation to childhood trauma and cognition.

The study by Theleritis et al. [43] showed that BDNF is related to childhood trauma but not to cognitive deficit in first break psychosis. This is the first study that investigates the association between childhood trauma and BDNF taking into account the variability of BDNF plasma levels in relation to antipsychotics. The investigators found an association between physical abuse and lower BDNF levels maintained a trend even when the effect of medication was calculated. BDNF levels were found to be higher for FEP (first episode psychosis) cases when compared to the control group for people who experienced physical or sexual abuse or premature death of either parent. No association of BDNF with cognitive measures was found.

Study Limitations

- Not only was the sample size in this study small, but also, it did not specifically assess for BDNFval66met polymorphism.
- The investigators were not able to explore the association between childhood trauma and BDNF with cognitive measures in a drug-naïve group of FEP; in the sample only 22 patients were drug-free and no meaningful statistical analysis could be applied on such a small subsample.
- The measurement of childhood trauma was based on participants' self-report, which could be subject to bias of under-reporting or over-reporting of events due to current symptoms, embarrassment, shame or social desirability.

We found one study that examined the relationship between BDNFval66met polymorphism, childhood trauma and cognition in chronic schizophrenics. In this study reported by Aas et al. [42] patients with psychosis not specifically with schizophrenia but also with bipolar disorder diagnoses were included and tested for BDNF polymorphism. The investigators found that BDNF Met carriers exposed to severe childhood sexual abuse showed reduced right hippocampal volume, larger right and left lateral ventricles and more profound cognitive impairments, specifically executive function/verbal fluency, working memory and verbal abilities. BDNF val66met modulates the association between childhood abuse, cognitive, and brain abnormalities in psychoses. Met carriers of the BDNF val66met with high level of childhood abuse showed more profound cognitive impairments (specifically executive function/verbal fluency, working memory and verbal abilities from WASI), as well as significant smaller hippocampus and larger ventricles, than all other groups. These findings were independent of age, sex, diagnosis, and intracranial volume (ICV), and were significant after correcting for number of cognitive tests, and brain measurements. The associations were strongest for working memory, executive function, as well as general IQ tasks from the WASI. The study population was Caucasian and therefore, no such information is available on any other ethnic groups.

Study Limitations

- No data for childhood trauma in healthy group.
- The data on childhood trauma was obtained retrospectively, resulting in a weakness which is inherent to retrospective reporting designs.
- Possibility that individuals with a compromised general cognitive function are more prone to childhood abuse and that the finding of an association between childhood abuse, cognitive and brain abnormalities may be due to underlying differences prior to abuse.

- Relatively small sample size and therefore unable to perform interactions investigating BDNF val66met, and other gene variants found to be related to childhood trauma and cognitive performance.

For further comparison of these studies, see Tables 2 and 3.

To the best of our knowledge there have been no studies in United States that try to address the interplay of BDNF and childhood trauma in cognitive impairment of schizophrenic patients. The study by Aas et al. [42] that was selected for this review was done in Sweden and the study by Theleritis et al. [43] which was selected for this review was done in UK.

Conclusion

There is an emerging body of evidence to suggest that there are gene-environment interactions that contribute to the development of schizophrenia. However, associations between the Val66Met polymorphism, childhood trauma and cognitive dysfunction in

Table 2 Comparison of methodology of studies selected

Study	Study design	Study group	Control	Exclusion criteria
Aas et al. [42]	Case control	Both inpatient and outpatient with chronic mental illness Caucasian Diagnosis of schizophrenia spectrum disorder, bipolar disorder and psychosis not otherwise specified Mean age 32.04 ± 11.40 years Total 106 participants	Without severe mental disorder or ongoing substance abuse Total 476 participants	Unstable or uncontrolled medical illness that interferes with brain functioning Age outside the range of 18–65
Theleritis et al. [43]	Case control	Patients presenting for the first time to psychiatric services with a functional psychotic illness—Psychotic symptoms lasting for at least 7 days Mean age 30.6 ± 9.3 Total of 87 patients	Healthy control group from the local population living in the area similar to the patient sample in age, gender, ethnicity, educational qualifications and employment status and recruited by means of internet and newspaper advertisements, and distribution of leaflets at train stations, shops and job centers Total of 152 controls	Presence of an organic psychosis A moderate or severe learning disability Pregnancy History of a medical or physiological cause of gonadal dysfunction (including hypothyroidism or other endocrine or metabolic disorder) Vascular disorders Neurological disorders Antipsychotic treatment longer than 30 days Lack of English fluency History of contact with health services for psychosis beyond the previous 6 months

Table 3 Comparison of assessment tools used in studies selected

Study	Cognition assessment	Childhood trauma assessment	Genetic assessment
Aas et al. [42]	Memory was measured using The California Verbal Learning test at immediate and delayed (30 min) time points Working memory was measured using the Letter–Number Sequencing, Digit Span forwards, and Digit Span backwards Executive functioning was assessed using the Color Word Interference Test (D-KEFS), with sub scores for interference control and interference set shifting Executive function was also measured using the Verbal Fluency Test [Delis–Kaplan Executive Function Scale (D-KEFS)] including phonetic fluency and semantic fluency Performance abilities (perception and visuospatial abilities)were measured using the Block Design task and the Matrix Reasoning from the WASI Verbal abilities were measured by Similarities and the Vocabulary from the WASI	Traumatic events in childhood were rated using a Norwegian version of the Childhood Trauma Questionnaire (CTQ)	The DNA was extracted from blood and genotyped using the Affymetrix Human SNP Array 6.0
Theleritis et al. [43]	Premorbid IQ [from the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001)] Verbal memory and learning (assessed using Logical Memory—Immediate and Delayed recall—from the Wechsler Memory Scale-III (WMS-III; Wechsler, 1997) Visual memory (from the Visual Reproduction—Immediate and Delayed recall—of the WMS-III) Executive function and working memory (Trail Making Test—part B, Spatial Span from the WMS-III and Digit Span from the WAIS-III) Attention, concentration and processing speed (Trail Making Test—part A and Digit Symbol from the WAIS-III) Verbal fluency (Semantic Fluency categories: 'body parts', 'fruits' and 'animals' and Letter Fluency: letters F, A, S tests)	Childhood traumatic events were assessed using the Childhood Experience of Care Abuse Questionnaire (CECA-Q)	No genetic assessment was done BDNF detected in plasma using Quantikine BDNF ELISA kit

schizophrenia have not been adequately addressed. There is a dearth of literature with findings that can be extrapolated to the general schizophrenia population. Considering the limitations of these studies, further research is necessary to obtain generalizable results for the better understanding and treatment of schizophrenia. The couple of studies that examined the abovementioned associations report almost contradictory results for interactions between BDNFval66met polymorphism, childhood trauma and schizophrenia. As current psychiatry is moving towards neurobiological basis of disorders, it is highly pertinent that further research in this area is conducted.

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Compliance with Ethical Standards

Conflict of Interest Dr. Geetanjali Sahu, Dr. Kishor Malavade, and Dr. Theresa Jacob declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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