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Brain-Derived Neurotrophic Factor and Psychiatric Disorders

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Abstract: ASD is a neurodevelopmental disorder that is characterized by social/communicative impairments and the presence of RRBs. The brain derived neurotrophic factor (BDNF) belongs to a family of neurotrophins that have a crucial role in survival and differentiation of neuronal populations during development. The expression of BDNF is regulated during transcription and translation, and also by posttranslational modifications. The presence of a complex multi-level regulation demonstrates the importance and diversity of BDNF functions. Transcription is controlled by multiple promoters that determine activity-dependent and tissue specific expression. Reduced levels of BDNF have been reported not only under normal aging conditions but also in pathological conditions including Huntington (HT), Alzheimer's disease (AD), and Parkinson's disease. However, the profile of cognitive deficits greatly differs between these pathologies according to the brain regions affected by degeneration. For example, the most profound BDNF deficits are reported in the hippocampus, parietal, entorhinal and frontal cortex for AD. There is previous speculation that BDNF may play a role in behavioral abnormalities and intellectual disability. In the last few years, evidence from animal models and clinical studies strongly suggest that dysregulation of neurotrophic factors could play an important role in the etiology of the bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia (SZ).

Keywords: *Brain-Derived Neurotrophic Factor, Psychiatric Disorders*

1. Introduction

ASD is a neurodevelopmental disorder that is characterized by social/communicative impairments and the presence of RRBs**.** While most ASD literature has largely focused on the social impairments associated with a diagnosis, recent research reflects a growing trend toward gaining a better understanding of RRBs **(1,2).**

RRBs in ASD are reliably grouped into two distinct categories: repetitive sensory motor behaviors and insistence on sameness behaviors**.** These categories are also sometimes referred to as lower-level and higher-level repetitive behaviors, respectively **(3).**

Repetitive sensory motor behaviors encompass stereotyped movements (such as hand flapping) and the repetitive use of specific objects (such as spinning objects), while insistence on sameness behaviors characterize ritualistic habits and a strict adherence to well established routines**.** A specific insistence on

sameness behavior that has been hypothesized as distinct from other RRBs is restricted interests. Restricted interests are defined as an interest or preoccupation with a particular object/topic or group of objects/topics, that is both abnormal in its specificity and the intensity with which it is expressed. Restricted interests in ASD have been likened to obsessions in OCD **(4)**

Male and female experiences of RRBs in ASD are fairly similar. Gender does not appear to be related to the tendency for RRBs to decrease with age nor do scores on RRB domains on tools like the ADI-R and the ADOS differ between male and female participants. On the other hand, OCD is characterized by the presence of time-consuming obsessions and/or compulsions that **cause** functional impairment. Unlike ASD, OCD is not characterized by marked language and cognitive impairments. Obsessions are persistent thoughts that are often experienced as unpleasant, irrational, and unwanted. At first glance, RRBs in ASD and OCD do not appear to differ greatly. Restricted interests/obsessions and repetitive sensory motor behaviors/compulsions are topographically quite similar. Moreover, the intrusive nature of RRBs are often found to be associated with social and functional impairments experienced both by individuals with ASD **(4)**

Before 2013, diagnosticians basing their diagnoses on the Diagnostic and Statistical Manual (DSM) system of the American Psychiatric Association were unable to give individuals with ASD a diagnosis of OCD and vice versa**.** However, some research indicates that this particular comorbid diagnosis has important clinical implications **(2).**

One study attempted to differentiate between OCD behaviors and repetitive sensory motor behaviors in two non-verbal adolescent boys with autism, while one participant exhibited ASD-like repetitive sensory motor behavior, the other participant's actions were more similar to compulsions **(5).**

The authors categorized each participant's behaviors as such based on definitions from reviewed literature and the topographies of each participant's behavior. They describe RRBs associated with an ASD diagnosis as stereotypical behaviors that are maintained by automatic reinforcement. This was evidenced through the first boy's lack of environmental context for his string-twirling behavior, which occurred often and caused interference with doing other things **(5).**

The second participant's behaviors included wiping tables and ordering/arranging objects. The authors described these behaviors as more "complex" than those exhibited by the first participant, and were in line with the DSM-IV definition of symptoms of OCD causing distress to whomever engages in these behaviors.

Measures of affect and heart rate during alternating phases of permitting and restricting engagement with RRBs revealed that the participant exhibiting OCD-like compulsions responded with increased heart rate after being restricted from his identified compulsive behavior (wiping a table scattered with salt). **(5).**

Given the fact that these physiological changes were not present in the participant exhibiting RRBs more similar to an ASD diagnosis, the authors posit that the combination of behavior description and measurement of physiological change may assist clinician's in distinguishing between disorder specific RRBs **(5).**

Although both OCD and ASD have similar symptoms, they are different conditions. OCD is a mental health disorder, whereas ASD is a developmental condition. ASD is a condition that a person is born with. OCD can develop during a person's lifetime. People with OCD tend to feel compelled to perform repetitive behaviors due to anxiety or distress, whereas autistic people may perform repetitive behaviors for enjoyment or to gain sensory input **(6).**

The brain derived neurotrophic factor (BDNF) belongs to a family of neurotrophins that have a crucial role in survival and differentiation of neuronal populations during development. The BDNF gene is localized to the boundary of chromosome 11p13 and 14. In the adult brain, BDNF also maintains high expression levels and regulates both excitatory and inhibitory synaptic transmission and activity-dependent plasticity **(7).**

The expression of BDNF is regulated during transcription and translation, and also by posttranslational modifications. The presence of a complex multi-level regulation demonstrates the importance and diversity of BDNF functions. Transcription is controlled by multiple promoters that determine activity-dependent and tissue specific expression **(8)**

Additionally, the expression of specific BDNF exons can be regulated by epigenetic mechanisms suggesting that environmental experiences dynamically influence mature BDNF levels **(9).**

Regarding the pattern of expression of BDNF in the brain, high levels of this molecule have been detected in the hippocampus, amygdala, cerebellum and cerebral cortex in both rodents and humans, with the highest levels found in hippocampal neurons **(10).**

Lower levels of BDNF have been detected in organs such as the liver, heart, lung, among others**.** The regulation of each transcript is controlled and/or modulated by factors like neuronal activity, exercise**,** antidepressants**,** stress**,** and hormones such as estrogens **(11).**

Brain derived neurotrophic factor is synthesized as the precursor pro BDNF, that can be stored in either dendrites or axons**,** and undergoes cleavage intra or extracellularly **(12)** to produce a mature BDNF protein.

BDNF is released in an activity dependent manner as a mixture of pro and mature BDNF**.** Interestingly, BDNF and pro BDNF are associated with opposing effects on cellular function, which gives BDNF protein function an additional level of complexity. The pro BDNF form is secreted under both pathological and non-pathological conditions. Pro BDNF preferentially binds p75 NTR receptor, which facilitates LTD and induces apoptosis **(13)**.

On the other hand, BDNF in its mature form binds specifically to tyrosine kinase receptors (TrkB) and promotes cell survivalfacilitates LTP and increases spine complexity **(14).**

Many studies have shown the critical role of BDNF for the regulation of plastic changes in the adult brain, including regulation of the trafficking phosphorylation and expression levels of NMDARs associated with augmented synaptic strength. Due to its critical role in LTP, BDNF has been postulated to be an essential part of the cellular mechanism supporting memory formation and maintenance by promoting synaptic consolidation **(15).**

BDNF and Alzheimer disease:

Reduced levels of BDNF have been reported not only under normal aging conditions but also in pathological conditions including Huntington (HT), Alzheimer's disease (AD), and Parkinson's disease. However, the profile of cognitive deficits greatly differs between these pathologies according to the brain regions affected by degeneration. For example, the most profound BDNF deficits are reported in the hippocampus, parietal, entorhinal and frontal cortex for AD and in the striatum and motor cortex for HT **(16).**

There is a substantial amount of studies supporting the idea that neurotrophic factors are crucial for the etiology of AD, in particular BDNF. BDNF protein and mRNA levels as well as proBDNF are reduced in the post-mortem brain of AD patients compared with age-matched controls, with no changes in TrkB levels **(17).**

This reduction was also reported in Mild Cognitive Impairment (MCI)**,** a potentially prodromal stage of AD. Furthermore, reduced circulating levels of BDNF were also found in MCI **(18).**

BDNF levels are correlated to the severity of the disease and with episodic memory performance in patients, suggesting that these decreases could be related to the pathogenesis of the disease. In conclusion, downregulation of BDNF and pro BDNF are thought to be an underlying mechanism related to early AD **(19).**

Neurodevelopmental disorders and BDNF:

There is previous speculation that BDNF may play a role in behavioral abnormalities and intellectual disability. In one study, 39 out of 54 patients with WAGR syndrome were reported to have intellectual disability **(20).**

The same study revealed that 24% of WAGR patients have ADHD and a similar incidence of ASD **Xu et al., (21)** found that deletion of BDNF among patients with WAGR syndrome occurred in 76.5% of patients with autism versus 42.3% in the group without autism suggesting that BDNF may modulate/influence the increased risk of autism in these patients **(22).**

Hashimoto et al., (23) showed reduced BDNF levels in adult male patients with autism as compared to age-matched healthy male control subjects. Another study showed that mean levels of BDNF were significantly lower in children with autism as compared to teenagers or adults, or to age matched healthy controls **(24).**

Other psychiatric disorders and BDNF:

In the last few years, evidence from animal models and clinical studies strongly suggest that dysregulation of neurotrophic factors could play an important role in the etiology of the bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia (SZ). Due to the role of BDNF in neural plasticity, there could be a link between BDNF expression and the cognitive symptoms associated with memory impairments **(25).**

The BD is a neuropsychiatric disorder that emerges from the interaction between genetic and environmental factors and is characterized by the switching between maniac and depressive episodes**.** It has been proposed that BDNF signaling participates in the physiological effects produced by some pharmacological treatments used for BD **(26).**

It has been shown that sBDNF decreases in the first episode of un medicated BD patients and that, after 1-year of pharmacological intervention, sBDNF concentration increases. In addition, there was a negative correlation between the number of episodes and sBDNF levels **(27).**

It has been reported that sBDNF positively correlates with the duration of the maniac and depressive episodes. This evidence suggests that episode-related changes in the structure of the brain could be linked to peripheral BDNF concentration **(9).**

Major depressive disorder is one of the most common mood disorders worldwide and is characterized by the absence of pursuit of pleasurable activities and the presence of negative thoughts**.** Since most common drugs used as antidepressant block the serotonin transporter (SERT), increasing extracellular serotonin in the raphe's nucleus post synapses it has been proposed that a misbalance in the serotonergic release could be related to the etiology of the depressive symptoms **(28).**

BDNF regulates the growth and reconstruction of 5-HT containing neuronal terminals in the cortex**)** and administration of BDNF in the raphe nucleus reduces behaviors related to depressive symptoms in rats **(29).**

In addition, MDD patients present cognitive decline in different domains including episodic memory but only recently these deficits have been studied in detail. A large amount of work shows that sBDNF is decreased in MDD **(30).**

Oral et al. (31) found that patients that recurrently present depressive episodes show lower levels of sBDNF compared with those patients that were cursing their first episode. Interestingly, antidepressant treatment increases sBDNF concentration **(30).**

Also, Brain-derived neurotrophic factor (BDNF) has been implicated in the pathogenesis of schizophrenia. It influences dopamine D3 receptor expression and elicits rapid postsynaptic effects on ion channels and NMDA receptors in hippocampus modulates the synaptic plasticity of DRD3-secreting neurons in the striatum **(32)**

BDNF gene encodes an activity-dependent endogenous neurotrophin which may promote the function and growth of 5-HT neurons in the brain and thus changes in BDNF protein levels, its receptor TrkB, or its mRNA expression in the hippocampus and cortical areas have been reported in patients with schizophrenia, suggesting that alterations in BDNF gene expression may be implicated in the pathogenesis of schizophrenia **(33)**

Besides, different studies have shown that the level of sBDNF correlates with cognitive performance in different domains in patients with schizophrenia**.** Despite the lack of consensus on whether basal sBDNF is increased or decreased in SZ patients**,** some studies have indicated a correlation between memory performance and sBDNF levels **(34).**

Interestingly, there are evidences that pro-cognitive effects of pharmacological interventions in SZ could be mediated by BDNF**.** For example, **Zhang et al. (35)** have found that a 12- week chronic treatment with olanzapine produced an increase in BDNF plasma concentration. Moreover, BDNF concentration positively correlated with cognitive performance in a RBANS scale of memory.

BDNF as a potential mediator underlying the benefits of therapeutic strategies:

Exogenous application of BDNF can restore the levels of hippocampal neurogenesis in aged animals**.** In the same way, exercise-induced increases in neurogenesis are necessary for the physical activity dependent enhancement in learning and memory **(36)**.

This led to the idea that neurogenesis could be the substrate of this cognitive enhancements mediated by BDNF**.** Another potential beneficial effect of BDNF is its ability to protect neurons from oxidative damage or excitotoxic stress and from Aβ-induced degeneration **(37)** in animal models of normal and pathological aging. In conclusion, several environmental and lifestyle interventions that reduce age-dependent cognitive decline and pathological degeneration can also increase BDNF production, suggesting that BDNF is neuroprotective. Given that cognitive training is a focused approach that selectively acts on sets of memory domains and that drugs are invasive, exercise is still a 'favorite' when thinking of potential therapeutic approaches **(9).**

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