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The BDNF Val66Met polymorphism enhances glutamatergic transmission but diminishes activity-dependent synaptic plasticity in the dorsolateral striatum

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Abstract

The Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene disrupts the activity-dependent release of BDNF, which might underlie its involvement in several neuropsychiatric disorders. Consistent with the potential role of regulated release of BDNF in synaptic functions, earlier studies have demonstrated that the BDNF Val66Met polymorphism impairs NMDA receptor-mediated synaptic transmission and plasticity in the hippocampus, the medial prefrontal cortex and the central amygdala. However, it is unknown whether the BDNF Val66Met polymorphism affects synapses in the dorsal striatum, which depends on cortical afferents for BDNF. Electrophysiological experiments revealed an enhanced glutamatergic transmission in the dorsolateral striatum (DLS) of knock-in mice containing the variant polymorphism (BDNF^{Met/Met}) compared to the wild-type (BDNF^{Val/Val}) mice. This increase in glutamatergic transmission is mediated by a potentiation in glutamate release and NMDA receptor transmission in the medium spiny neurons without any alterations in non-NMDA receptor-mediated transmission. We also observed an impairment of synaptic plasticity, both long-term potentiation and depression in the DLS neurons, in BDNF^{Met/Met} mice. Thus, the BDNF Val66Met exerts an increase in glutamatergic transmission but impairs synaptic plasticity in the dorsal striatum, which might play a role in its effect on neuropsychiatric symptoms.

Keywords

Dorsal striatum; BDNF Val66Met; NMDA receptors; Synaptic plasticity; Glutamate

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1. Introduction

Emerging evidence suggests that brain-derived neurotrophic factor (BDNF) plays an important role in the function of the dorsal striatum, a brain structure involved in goal-directed and habitual behaviors (Baydyuk et al., 2011; Rauskolb et al., 2010; Yin and Knowlton, 2006). Consistently, alterations in striatal BDNF-TrkB signaling have been implicated in maladaptive behaviors such as compulsive drug use and neurodegenerative diseases particularly Huntington's disease (Bahi and Dreyer, 2013; Im et al., 2010; Krasnova et al., 2013; McGough et al., 2004). Unlike the cortex and hippocampus, which express BDNF, the striatum does not express high levels of BDNF but receives BDNF primarily from the cortical afferents by anterograde transport (Altar et al., 1997; Conner et al., 1997; Fumagalli et al., 2007). Interestingly, the striatum expresses high levels of TrkB, the receptor for BDNF (Freeman et al., 2003). Given the profound effect of BDNF on synapses, a reduction in BDNF availability from the cortical afferents could alter striatal synapses (Jeanblanc et al., 2009; Milnerwood and Raymond, 2010; Simpson et al., 2010). Conversely, an elevation in cortical BDNF enhances plasticity in the striatum and reverses striatal deficits in mouse models of Huntington's disease (Jia et al., 2010; Xie et al., 2010).

The human single-nucleotide polymorphism (SNP) in the BDNF gene, a methionine (Met) substitution for valine (Val) at codon 66 (Val66Met), has been implicated in cognitive dysfunction, anxiety disorders, fear extinction deficit and substance abuse (Chen et al., 2006; Cheng et al., 2005; Egan et al., 2003; Hariri et al., 2003; Hou et al.; Hwang et al., 2006; Jeanblanc et al., 2009; Jiang et al., 2005; Lang et al., 2007; Novak et al.; Pattwell et al., 2012; Schumacher et al., 2005; Soliman et al., 2010; Terracciano et al., 2010; Wojnar et al., 2009). Consistently, the BDNF Val66Met SNP impairs synaptic plasticity in the infralimbic medial prefrontal cortex, the hippocampus and the central amygdala (Bath et al., 2012; Galvin et al., 2015; Ninan et al., 2010; Pattwell et al., 2012). However, it is unknown whether the Val66Met affects synaptic function in the corticostriatal pathway, the impairment of which has been implicated in not only anxiety disorders but also drug abuse (Fumagalli et al., 2007; Furman et al., 2011; Im et al., 2010; Jeanblanc et al., 2009; McGough et al., 2004; Pittenger et al., 2011). The BDNF Val66Met SNP facilitates the extinction of cocaine seeking, and high frequency of Val allele carriers were observed among individuals addicted to methamphetamine (Briand et al., 2012; Cheng et al., 2005). However, a higher frequency of Met allele carriers is linked to smoking and high alcohol intake (Colzato et al., 2011; Lang et al., 2007). Also, the BDNF Val66Met SNP has been shown to affect motor behavior (McHughen et al., 2010). Given the effect of the BDNF Val66Met SNP on the activity-dependent release of BDNF, we tested whether this polymorphism affects glutamatergic transmission in the dorsolateral striatum (DLS), a brain region implicated in habitual drug use and anxiety disorders (Chen et al., 2006; Packard, 2009; Schneck and Vezina, 2012; Yin and Knowlton, 2006). We observed an enhanced glutamatergic transmission in the DLS of BDNF^{Met/Met} mice, which involved an increase in glutamate release and NMDA receptor-mediated currents. Furthermore, we observed an impairment of synaptic plasticity in the corticostriatal pathway of BDNF^{Met/Met} mice suggesting a profound effect of the BDNF Val66Met SNP on the dorsal striatum.

2. Methods and materials

2.1. Animals

Male BDNF^{Met/Met} mice and BDNF^{Val/Val} littermates derived from heterozygous BDNF^{+ /Met} parents were used for all experiments. All animals were kept on a 12:12 light–dark cycle at 22°C with food and water available *ad libitum*. All experiments were performed in accordance with institutional guidelines. Mice were genotyped as described previously (Chen et al., 2006).

2.2. Electrophysiology

Extracellular recording—2–3 month old mice were decapitated after pentobarbital anesthesia. Coronal brain slices (300 μ m) were made on a vibratome (Campden Instruments) and submerged in artificial cerebrospinal fluid (ACSF) containing (in mM): NaCl (118), KCl (2.5), glucose (10), NaH₂PO₄ (1), CaCl₂ (3), MgCl₂ (2) and NaHCO₃ (25) bubbled with 95% O₂/5% CO₂ (pH 7.4), in a brain-slice keeper for at least 60 min at room temperature before transferring to the recording chamber. Bicuculline (10 μ M) was included in the recording solution. Recording electrodes were filled with 2 M NaCl solution, and population spikes were recorded from the striatum with the IE-210 amplifier (Warner Instruments) using Digidata 1440A and pCLAMP 10 software (Molecular Devices) at 32 °C. For synaptic stimulation, a bipolar electrode was placed in the white matter between the cortex and the DLS to activate corticostriatal fibers (Shmelkov et al., 2010; Yin et al., 2009). The population spike amplitude was calculated as the mean of the amplitude from the first peak positivity to the peak negativity of the population spike and the amplitude of the peak negativity of the population spike to the second peak positivity (Alger and Teyler, 1976; Lovinger et al., 1993). Paired-pulse responses were evoked at inter-stimulus intervals of 20, 40, 80, 120 and 250 ms using a stimulation intensity of 0.9 mA (Shmelkov et al., 2010). The paired-pulse ratio is defined as the ratio of second population spike amplitude to the first population spike amplitude. LTP was induced by 100Hz stimulation (4 times at 10sec interval in Mg²⁺ free solution) whereas LTD was induced by the same protocol in the presence of Mg²⁺ (Kitada et al., 2007). Population spike amplitudes were analyzed by Clampfit software (Molecular Devices).

Whole cell recording—One month old mice were killed by decapitation. The brains were quickly removed and placed in ice-cold ACSF consisting of (in mM): NaCl (118), KCl (2.5), CaCl₂ (2), MgCl₂ (2), NaHCO₃ (26), NaH₂PO₄ (1), D-glucose (10), osmolarity adjusted to 325 mOsm and aerated by 95% O₂/ 5% CO₂ (pH 7.4). Coronal brain slices (300 μ m) were cut using a vibratome (Campden Instruments) and kept submerged in ACSF in a slice pre-incubator (Scientific System Design Inc. Canada) at room temperature for at least 60 min to allow recovery. A single slice was then transferred to a recording chamber, which was held submerged by a nylon net at 32°C with a TC324B in-line solution heater and controller (Warner Instruments, CT). The chamber was continuously perfused by ACSF at a constant rate of 2 ml/min. The DLS MSNs were visualized using video-enhanced infrared differential interference contrast microscopy (Hamamatsu C5405) with an Olympus BX50WI upright microscope fitted with a 40x long working distance water-immersion objective. Patch electrodes (4–6 M Ω) were pulled from borosilicate capillary glass (World Precision

Instruments, Sarasota, FL) with a Heka pipette puller (PIP5). For the rectification index experiments, whole-cell patch clamp recordings were made from the DLS MSNs in the presence of bicuculline (10 μ M) and NMDA receptor blocker D-2-Amino-5-phosphonovaleric acid (APV, 50 μ M) in the extracellular solution. The electrode solution contained (in mM): CsCl (130), HEPES (10), EGTA (0.5), QX-314 (5), Mg^{2+} -ATP (2), GTP (0.2) and spermine (0.1) (Osmolarity is adjusted to 290 mOsm with sucrose, and pH is adjusted to 7.4 with CsOH.). We have obtained several points of the current–voltage relationship (holding V_m at -70 , -60 , -50 , -40 , -30 , -20 , -10 , 0 , $+10$, $+20$, $+30$ and $+40$ mV). For synaptic stimulation, we placed bipolar electrodes in the white matter between the cortex and the DLS to activate corticostriatal fibers (Shmelkov et al., 2010; Yin et al., 2009). The rectification index was expressed as the ratio of EPSC amplitudes: $EPSC_{-70\text{ mV}}/EPSC_{+40\text{ mV}}$ (Ninan, 2011). Non-NMDA miniature EPSCs (mEPSCs) were recorded at -60 mV in the presence of bicuculline (10 μ M) and tetrodotoxin (1 μ M) using an electrode solution containing the following (in mM): potassium gluconate (130), KCl (10), $MgCl_2$ (5), MgATP (5), GTP (0.2), EGTA (0.5), HEPES (5), pH adjusted to 7.4 with KOH. NMDA mEPSCs were recorded in the presence of bicuculline, tetrodotoxin, glycine (10 μ M), strychnine (1 μ M, to block the potential activation of glycine receptors) and a non-NMDA receptor blocker, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione (NBQX, 10 μ M) in the absence of Mg^{2+} at -60 mV (Atasoy et al., 2008). For the NMDA/AMPA ratio measurements, an extracellular solution containing bicuculline and an electrode solution consisting of (mM): CsCl (130), HEPES (10), EGTA (0.5), QX-314 (5), GTP (0.2) and MgATP (5) were used. The NMDA/AMPA ratio was calculated by dividing the amplitude of the NMDA current measured at 50 ms after the peak at $+40$ mV by the AMPA current measured at the peak response at -60 mV (Myme et al., 2003). Recordings were rejected when the series resistance or holding current changed by 10%. Recordings were made using an Axopatch 200B amplifier (Molecular Devices, CA) and digitized by Digidata 1440A (Molecular Devices, CA). Evoked responses were analyzed by Clampfit software (Molecular Devices). mEPSCs were analyzed by the Mini Analysis software from Synaptosoft, Inc. (GA).

2.3. Modified rapid Golgi impregnation

In order to study the dendritic morphology of MSNs, we employed a modified rapid Golgi impregnation method. Briefly, 10 male P90 BDNF^{Met/Met} and BDNF^{Val/Val} mice were deeply anesthetized using Euthasol (0.1 ml/10 g body weight). Brains were removed immediately and submerged in a modified Golgi-cox solution containing 1% mercuric chloride, 1% potassium dichromate and 0.8% potassium chromate (15 ml/brain). Sample bottles were placed in dark at room temperature for 10 days, and then transferred to 30% sucrose in water at 4°C for at least 3 days. Impregnated brains were cut into 120 μ m serial coronal sections, collected in 0.3% gelatin and serial sections were mounted immediately onto 0.3% gelatin coated slides. Sections were brushed with 50% sucrose, and allowed to air dry for 3 days in the dark. Slides were washed three times with DD water for 10 min before transferring into a blackening solution containing 0.4% potassium hydroxide for 10–15 min. After washing with water, slides were dehydrated using alcohol (50–100%). Then sections were cleared using Histo-Clear. Slides were cover-slipped using mounting medium DPX and air-dried in the dark for 3 days before examining under a light microscope.

Dendritic complexity analysis was carried out using the NeuroExplorer Program (MicroBrightField, VA USA). MSNs included in the analysis satisfied the following criteria: (i) an isolated cell body with a clear relationship of the primary dendrite to the soma, (ii) a presence of untruncated dendrites, (iii) consistent and dark impregnation along the extent of all of the dendrites, and (iv) little overlap with the neighboring impregnated cells (Chen et al., 2006). For each included neuron, cell body and dendritic branches were 3D reconstructed under 40x magnification. Spine types and density were measured under a 100x oil lens (Hering and Sheng, 2001; Risher et al., 2014).

2.4. Data analysis

Results were expressed as mean $\pm$ Standard Error Mean (SEM). Input-output measurements, paired pulse ratio, synaptic plasticity and dendritic complexity data were analyzed using two-way repeated measures ANOVA. EPSCs were compared using t-test. Sidak's multiple comparisons test was used for dendritic spine analysis. The level of significance was $p < 0.05$.

3. Results

3.1. Corticostriatal glutamatergic transmission is enhanced in BDNF^{Met/Met} mice

To test whether the BDNF Val66Met affects corticostriatal glutamatergic transmission, we examined population spike amplitudes in the DLS of BDNF^{Met/Met} and BDNF^{Val/Val} mice. We observed a significant enhancement of population spike amplitude in the DLS of BDNF^{Met/Met} mice compared to the BDNF^{Val/Val} mice suggesting an enhancement of corticostriatal glutamatergic transmission in the DLS of BDNF^{Met/Met} mice (Fig. 1A). Next, we examined whether a pre-synaptic mechanism is involved in the enhancement of corticostriatal neurotransmission in the DLS of BDNF^{Met/Met} mice. Paired pulse facilitation is a short-term plasticity believed to depend on pre-synaptic mechanisms (Hess et al., 1987; Zucker, 1989). Therefore, we studied the paired pulse ratio of population spike amplitude in the DLS of BDNF^{Met/Met} and BDNF^{Val/Val} littermates. We observed a significant decrease in paired pulse ratio in BDNF^{Met/Met} mice compared to the BDNF^{Val/Val} mice suggesting an enhanced glutamate release in the DLS of BDNF^{Met/Met} mice (Fig. 1B). Thus, the increased population spike amplitude in the DLS of BDNF^{Met/Met} mice might be mediated by an enhanced glutamate release from the cortical afferents.

To further confirm the enhancement of glutamate release in the DLS of BDNF^{Met/Met} mice, we studied mEPSCs from the DLS MSNs. We observed a significantly higher mEPSC frequency but not amplitude in the DLS MSNs of BDNF^{Met/Met} mice compared to the BDNF^{Val/Val} mice (Figs. 2A–C). The increase in mEPSC frequency without the modification of the mEPSC amplitude and the decreased paired pulse ratio (Fig. 1B) suggests an enhancement of glutamate release in BDNF^{Met/Met} mice.

In addition to an enhanced glutamate release, a post-synaptic mechanism could play a role in the potentiation of synaptic transmission. A well-established mechanism involved in the potentiation of glutamatergic transmission is the synaptic insertion of GluA2 subunit-lacking calcium permeable AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)

receptors (CP-AMPA) (Conrad et al., 2008). Synaptic insertion of CP-AMPA shows significant inward rectification (Donevan and Rogawski, 1995). However, we did not observe any significant difference in the inward rectification of non-NMDA EPSCs between BDNF^{Met/Met} and BDNF^{Val/Val} littermates (Figs. 3A–C), suggesting that synaptic insertion of CP-AMPA is unlikely to be involved in the enhancement of corticostriatal glutamatergic transmission in the DLS of BDNF^{Met/Met} mice. The absence of a modification of inward rectification as well as lack of change in mEPSC amplitude strongly suggests that the post-synaptic non-NMDA receptors in the DLS MSNs are not affected by the BDNF Val66Met polymorphism.

3.2. BDNF^{Met/Met} mice show enhanced NMDA receptor neurotransmission in the DLS MSNs

Given the lack of effect on baseline non-NMDA receptor neurotransmission but enhanced glutamate release in the DLS MSNs of BDNF^{Met/Met} mice, we asked whether NMDA receptor neurotransmission is modified in the DLS MSNs of BDNF^{Met/Met} mice. We compared NMDA mEPSCs in BDNF^{Met/Met} and BDNF^{Val/Val} littermates. Consistent with an increase in non-NMDA mEPSC frequency and a decrease in paired pulse ratio (Figs. 1B, 2B), we observed a significant increase in NMDA mEPSC frequency in BDNF^{Met/Met} mice compared to the BDNF^{Val/Val} littermates (Figs. 4A,B). In contrast to the lack of effect on non-NMDA mEPSC amplitude, the NMDA mEPSC amplitude was significantly higher in BDNF^{Met/Met} mice (Figs. 4A,C). These results suggested that the DLS-MSNs of BDNF^{Met/Met} mice exhibit an enhanced NMDA receptor neurotransmission. To further confirm the enhanced NMDA receptor neurotransmission in BDNF^{Met/Met} mice, we analyzed the evoked EPSCs in the DLS MSNs of BDNF^{Met/Met} and BDNF^{Val/Val} littermates. Given the enhanced glutamate release in the DLS MSNs of BDNF^{Met/Met} mice, a measurement of absolute NMDA EPSC amplitude is not ideal. Therefore, we measured the NMDA/AMPA EPSC ratio in the DLS MSNs, which nullified the effect of altered glutamate release on EPSCs. Consistent with the increase in NMDA mEPSC amplitude in BDNF^{Met/Met} mice (Figs. 4A,C), we observed a significantly higher NMDA/AMPA EPSC ratio in BDNF^{Met/Met} mice confirming that the NMDA receptor neurotransmission is enhanced in the DLS MSNs of BDNF^{Met/Met} mice (Figs. 4D,E).

3.3. Dendritic complexity and spine density in the DLS MSNs of BDNF^{Met/Met} mice

To understand whether morphological changes in MSNs contributed to a modification of synaptic transmission, we compared dendritic complexity in the DLS MSNs of BDNF^{Val/Val} and BDNF^{Met/Met} mice using the Sholl analysis as described earlier (Chen et al., 2006). We did not observe a statistically significant difference in dendritic complexity between BDNF^{Val/Val} and BDNF^{Met/Met} groups (Figs. 5A,B). Also, an analysis of the fractal dimension of dendritic branches revealed no significant difference between BDNF^{Val/Val} and BDNF^{Met/Met} groups (Fig. 5C). These results suggest that the BDNF Val66Met polymorphism does not affect the dendritic development of MSNs in the DLS.

Next we compared spine morphology and density in the DLS MSNs of BDNF^{Val/Val} and BDNF^{Met/Met} mice. Although we observed an increase in the density of thin spines and a decrease in the density of mushroom-shaped spines in the BDNF^{Met/Met} group, the total spine density remained unaffected (Figs. 6A,B). The dendritic complexity and spine density

data suggest that morphological changes might not have contributed to the observed changes in synaptic transmission in BDNF^{Met/Met} mice.

3.4. Impairment of activity-dependent plasticity in the DLS of BDNF^{Met/Met} mice

Our earlier studies have demonstrated an impairment of synaptic plasticity in the hippocampus, the medial prefrontal cortex and the amygdala by the BDNF Val66Met polymorphism (Bath et al., 2012; Galvin et al., 2015; Ninan et al., 2010; Pattwell et al., 2012). Since corticostriatal plasticity depends upon BDNF-TrkB signaling (Jia et al., 2010), we asked whether the BDNF Val66Met affects synaptic plasticity in the dorsal striatum. An application of a 100Hz stimulation in the absence of magnesium produced a robust and long-lasting enhancement of population spike amplitude in the BDNF^{Val/Val} group, while the BDNF^{Met/Met} group exhibited a significantly lower potentiation of population spike amplitude (Fig. 7A). We also examined whether activity-dependent long-lasting depression in the DLS is affected by the BDNF Val66Met polymorphism. A 100Hz stimulation in the presence of magnesium produced a long-lasting depression of population spike amplitude in the BDNF^{Val/Val} group (Fig. 7B). However, the long-lasting depression in the BDNF^{Met/Met} group was significantly lower than BDNF^{Val/Val} group (Fig. 7B). These results suggest that an impairment of the activity-dependent release of BDNF diminishes plasticity in the DLS.

4. Discussion

Our results show that the BDNF Val66Met polymorphism enhances corticostriatal neurotransmission in the DLS which involves an increase in glutamate release and NMDA receptor-mediated neurotransmission in the MSNs without affecting AMPA receptor-mediated transmission. The current results are surprising given the role of BDNF in positively modulating neurotransmitter release and post-synaptic NMDA and AMPA receptors (Alder et al., 2005; Caldeira et al., 2007; Itami et al., 2003; Levine et al., 1998; Li et al., 1998; Narisawa-Saito et al., 1999; Slipczuk et al., 2009; Yano et al., 2006). A similar enhancement of glutamatergic neurotransmission in the striatal MSNs has been observed in animal models for Huntington's disease which express mutated huntingtin (Milnerwood and Raymond, 2010). Mutated huntingtin is known to alter BDNF availability in the striatum by decreasing either the transcription or the anterograde transport of BDNF in cortical neurons (Gauthier et al., 2004; Zuccato et al., 2001; Zuccato et al., 2003). Therefore, it is possible that a decrease in the activity-dependent release of BDNF from the cortical terminals in BDNF^{Met/Met} mice results in an enhancement of glutamatergic neurotransmission in the MSNs. However, the mechanism of increased glutamatergic neurotransmission in response to decreased BDNF in the striatum is unclear. The lack of changes in dendritic complexity and spine density suggests that morphological changes are unlikely to be responsible for changes in synaptic transmission in BDNF^{Met/Met} mice. These results are consistent with the earlier studies showing an absence of an effect of the BDNF Val66Met polymorphism on striatal volume (Yu et al., 2009). However, the BDNF Val66Met reduces volume and dendritic complexity in the hippocampus and medial prefrontal cortex (Chen et al., 2006; Yu et al., 2009).

The striatum contains two distinct circuits, the direct pathway comprised of dopamine D₁ receptor expressing MSNs and the indirect pathway comprised of MSNs expressing D₂ receptors (Kreitzer and Malenka, 2008). It is plausible that an altered balance between the direct and indirect pathways as a result of a diminished function of predominantly TrkB rich dopamine D₂ receptor-positive MSNs in BDNF^{Met/Met} mice could facilitate cortical input to the striatum by disinhibiting thalamocortical projections (Baydyuk et al., 2011; Kreitzer and Malenka, 2008). Human BDNF Val66Met carriers show a reduced D2 receptor density in the striatum (Montag et al., 2010). Also, it is possible that a reduction in the activity-dependent release of BDNF in BDNF^{Met/Met} mice could influence dopamine release in the striatum and thus altering glutamate receptor neurotransmission (Andre et al., 2010; Bosse et al., 2012; Dluzen et al., 2002). Also, future studies will be necessary to determine whether the elevated glutamatergic transmission in the BDNF^{Met/Met} mice is due to an impairment of a proBDNF-induced negative regulation of glutamatergic transmission (Yang et al., 2014). An altered interaction of the variant Met66 prodomain with neurotrophin receptors or co-receptors might influence synaptic transmission (Anastasia et al., 2013). Consistent with the BDNF Val66Met-induced impairment of synaptic plasticity in the hippocampus, medial prefrontal cortex and amygdala, activity-dependent synaptic plasticity was impaired in the DLS of BDNF^{Met/Met} mice which strongly supports the role of the activity-dependent release of BDNF in synaptic plasticity. Congruent with an impaired synaptic plasticity in the DLS, the BDNF Val66Met polymorphism is associated with abnormal motor skills (Morin-Moncet et al., 2014). Also, Parkinson's patients with the BDNF Met allele exhibit significantly higher levodopa-induced dyskinesia due to a possible alteration of synaptic plasticity in the striatum (Foltynie et al., 2009).

An interesting possibility is that the enhanced corticostriatal neurotransmission observed in our study might be a key mechanism in the competition between multiple memory systems (Chang and Gold, 2003; Lee et al., 2008; Schroeder et al., 2002). Both human and animal studies have shown that hippocampus- and striatum-dependent memory systems compete with each other (Lee et al., 2008; Poldrack et al., 2001). Consistent with the human studies showing a hippocampal dysfunction in Val66Met carriers, BDNF^{Met/Met} mice exhibited an impairment of hippocampus-dependent memory as well as NMDA receptor transmission (Chen et al., 2006; Ninan et al., 2010). On the other hand, human studies have shown that the BDNF Met66 allele was associated with a better cognitive performance in the psychomotor and motor domains (Oroszi et al., 2006). Furthermore, BDNF Val66Met carriers preferentially employ a caudate nucleus-dependent strategy over a hippocampus-dependent spatial strategy in navigation tasks (Banner et al., 2011). Consistent with these human studies, BDNF^{Met/Met} mice exhibit a better motor recovery following chronic stroke compared to BDNF^{Val/Val} mice (Qin et al., 2014). Thus, the enhanced glutamatergic synaptic transmission might underlie the dominant striatum-dependent function in BDNF Val66Met carriers.

A diminished synaptic function in the cortex and hippocampus and an increased strength of glutamatergic synapses in the striatum might play a significant role in the effect of BDNF Val66Met on anxiety symptoms and drug abuse (Bath et al., 2012; Ninan et al., 2010; Pattwell et al., 2012). Because of this region-specific modulation of synapses by the BDNF Val66Met SNP, it is possible that habit-driven stimulus-response behaviors mediated by the

highly active striatum in BDNF Val66Met carriers dominate over goal-directed behaviors (Pittenger, 2013). Consistent with an increased engagement of DLS in drug seeking behavior (Corbit et al., 2012), the BDNF Val66Met SNP was associated with a higher risk and an earlier occurrence of relapse among patients treated for alcohol dependence (Wojnar et al., 2009). Also, it was reported that BDNF Val66Met carriers are more vulnerable to initiate and maintain smoking (Lang et al., 2007). In agreement with the increased anxiety-like behaviors and the differential modulation of dorsal striatal and hippocampal synapses in BDNF Val66Met carriers (Chen et al., 2006; Ninan et al., 2010), a pharmacological induction of anxiety-like symptoms preferentially engages dorsal striatum-dependent habit memory while impairing hippocampal functions (Packard, 2009). Given the potential role of the dorsal striatum in obesity (Nummenmaa et al., 2012), an overactive dorsal striatum might play a role in obesity in BDNF Val66Met carriers (Beckers et al., 2008; Skledar et al., 2012). A recent study also suggested a possible interaction between smoking and body mass index in BDNF Val66Met carriers (Hong et al., 2012). In all, our study suggests a synaptic mechanism by which the BDNF Val66Met polymorphism might exert its effects on anxiety symptoms and comorbid disorders including drug abuse and obesity.

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Figure 1.

A) BDNF^{Met/Met} mice exhibit an enhanced corticostriatal neurotransmission. Average population spike amplitudes in the DLS of BDNF^{Met/Met} (n=17 slices/7 mice) and BDNF^{Val/Val} littermates (n=19 slices/7 mice). Population spike amplitude was significantly higher in BDNF^{Met/Met} mice ($F(1,34)=7.2$, $P=0.01$). Left panel shows examples of population spikes in response to 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9mA stimulation. **B)** Average paired pulse ratio in the DLS of BDNF^{Met/Met} (n=11 slices/7 mice) and BDNF^{Val/Val} littermates (n=11 slices/7 mice). BDNF^{Met/Met} mice show decreased paired pulse ratio in the DLS suggesting enhanced glutamate release ($F(1,100)=10.83$, $P=0.001$). Upper panel shows examples of population spikes in response to stimulation at inter-stimulus intervals of 20, 40, 80, 120 and 250ms.

Figure 2. BDNF^{Met/Met} mice show increased glutamate release in the DLS. **A)** Examples of mEPSCs in the DLS MSNs of BDNF^{Met/Met} and BDNF^{Val/Val} littermates. **B&C)** Average mEPSC frequency and amplitude in the DLS MSNs of BDNF^{Met/Met} (n=13 cells/4 mice) and BDNF^{Val/Val} littermates (n=13 cells/4 mice). The mEPSC frequency ($t(24) = -2.82$, $P = 0.009$) but not amplitude ($t(24) = -0.54$, $P = 0.59$) was significantly higher in BDNF^{Met/Met} mice suggesting enhanced glutamate release onto the MSNs.

Figure 3.

The increased corticostriatal neurotransmission in BDNF^{Met/Met} mice does not involve synaptic insertion of calcium permeable AMPA receptors. **A)** Examples of EPSCs recorded at -70, -60, -50, -40, -30, -20, -10, 0, +10, +20, +30 and +40 mV in the DLS MSNs of BDNF^{Met/Met} and BDNF^{Val/Val} littermates. **B)** Current-voltage plot of EPSCs in BDNF^{Met/Met} and BDNF^{Val/Val} littermates. **C)** Average rectification index in BDNF^{Met/Met} (n=8 cells/3 mice) and BDNF^{Val/Val} littermates (n=7 cells/3 mice). We did not observe any significant difference in inward rectification of EPSCs in the DLS MSNs of BDNF^{Met/Met} and BDNF^{Val/Val} littermates suggesting absence of enhanced synaptic insertion of GluA2 lacking calcium permeable AMPA receptors in BDNF^{Met/Met} mice ($t(13)=0.8$, $P=0.4$).

Figure 4.

The DLS MSNs of BDNF^{Met/Met} mice exhibit enhanced NMDA receptor neurotransmission. **A)** Examples of NMDA mEPSCs in the DLS MSNs of BDNF^{Met/Met} and BDNF^{Val/Val} littermates. **B&C)** Average NMDA mEPSC frequency and amplitude in the DLS MSNs of BDNF^{Met/Met} (n=7 cells/4 mice) and BDNF^{Val/Val} littermates (n=7 cells/4 mice). Both the NMDA mEPSC frequency (t(12)=4.8, P=0.001) and amplitude (t(12)=4.7, P=0.001) were significantly higher in BDNF^{Met/Met} mice suggesting enhanced glutamate release and NMDA receptor neurotransmission. **D)** Examples of EPSCs recorded at -60 and +40mV in the DLS MSNs of BDNF^{Met/Met} and BDNF^{Val/Val} littermates. Dotted lines represent time points at which NMDA receptor and AMPA receptor currents were measured. **E)** Average NMDA/AMPA ratio in BDNF^{Met/Met} (n=7 cells/3 mice) and BDNF^{Val/Val} littermates (n=8 cells/3 mice). The NMDA/AMPA ratio was significantly higher (t(13)=1.8, P=0.04) in the DLS MSNs of BDNF^{Met/Met} mice suggesting enhanced NMDA receptor neurotransmission in BDNF^{Met/Met} mice.

Figure 5.

Dendritic complexity in the DLS MSNs of BDNF^{Met/Met} mice. **A)** Representative traces of Golgi-stained DLS MSNs from BDNF^{Met/Met} and BDNF^{Val/Val} mice. **B)** Sholl analysis of DLS MSNs from BDNF^{Met/Met} (n=20) and BDNF^{Val/Val} (n=20) groups ($F(1,684)=0.73$, $P=0.39$). **C)** Fractal dimension of dendritic branches in BDNF^{Met/Met} and BDNF^{Val/Val} groups ($t(38)=1$, $P=0.3$).

Figure 6.

Spine density in the DLS MSNs of BDNF^{Met/Met} mice. **A)** Representative images of Golgi-stained dendritic spines in the DLS MSNs from BDNF^{Met/Met} and BDNF^{Val/Val} mice. **B)** Density of different types of dendritic spines in the DLS MSNs of BDNF^{Met/Met} and BDNF^{Val/Val} mice. Sidak's multiple comparisons test revealed significantly higher number of thin spines and reduced number of mushroom spines in BDNF^{Met/Met} mice. However, there was no statistically significant difference in total number of dendritic spines between BDNF^{Met/Met} (n=20) and BDNF^{Val/Val} (n=20) groups.

Figure 7.

Impairment of synaptic plasticity in the DLS of BDNF^{Met/Met} mice. **A)** Long-lasting potentiation of population spike amplitude is impaired in BDNF^{Met/Met} group (n=8 slices/4 mice) compared to BDNF^{Val/Val} group (n=8 slices/4 mice) ($F(1,14)=5.3$, $P=0.037$). Upper panel shows examples of population spikes before and at 50 min after the high frequency stimulation. **B)** Long-lasting depression of population spike amplitude is impaired in BDNF^{Met/Met} group (n=9 slices/4 mice) compared to BDNF^{Val/Val} group (n=9 slices/4 mice)

($F(1,16)=13.6$, $P=0.002$). Upper panel shows examples of population spikes before and at 50 min after the high frequency stimulation.

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