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Exploring Brain-Derived Neurotrophic Factor Val66Met Polymorphism and Extinction Learning–Based Treatment Outcome in Obsessive-Compulsive Disorder:

A Pilot Study

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To the Editors:

A common single-nucleotide polymorphism (SNP) in the human brain-derived neurotrophic factor (BDNF) gene (Val66Met; rs6265) has been reported to alter extinction learning in human carriers and knock-in mice with the SNP.[1] Extinction learning is a major component of behavioral therapies for anxiety disorders, and medication thought to enhance extinction learning may facilitate cognitive-behavioral therapy (CBT) gains.[2] Our recent, open-label pilot study in unmedicated obsessive-compulsive disorder (OCD) subjects (N = 10) found that abbreviated CBT (10 one-hour exposure sessions), delivered during the 2 weeks when ketamine putatively facilitates extinction learning, helps individuals maintain ketamine-related improvement.[3] To refine our understanding of the role of BDNF, we performed a secondary analysis to explore whether the BDNF Val66Met polymorphism is associated with treatment response to either exposure-based CBT or ketamine. Given the BDNF Met allele impairs activity-dependent BDNF secretion that is critical for extinction learning,[4-6] we hypothesized that patients without the BDNF Met allele would have a better OCD outcome than BDNF Met allele carriers.

With institutional review board approval, 10 unmedicated outpatients with OCD (*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*) (ages 18–55) were recruited and provided written informed consent before participation. Participants had at least moderate symptoms [score ≥16 on the Yale-Brown Obsessive-Compulsive Scale (YBOCS)].[7] Of 10 subjects with OCD, 4 (40%) had no other psychiatric comorbidity. Four subjects met criteria for comorbid major depression, and 1 subject met criteria for dysthymia; all had mild to moderate depression (Hamilton Depression Rating Scale–17 item scores were between 13 and 16). One subject met criteria for general anxiety disorder. The mean number of prior adequate serotonin reuptake inhibitor trials was 1.8 (SD, 2.1), and 60% failed at least 1 prior adequate trial of CBT with exposure and response prevention. DNA was extracted from blood using the QIAmp DNA Blood Kit (Qiagen) and used as a template for amplification of the *BDNF* genomic portion that harbors the BDNF Val66Met (primer sequences are available on request). Polymerase chain reaction fragment was digested with restriction endonuclease *Nla*III (New England Biolabs Inc, Boston, Massachusetts) and resolved in 2% UltraPure Agarose (Invitrogen, Carlsbad California). Participants received a single 40-minute ketamine infusion (dose, 0.5 mg/kg) and then completed 10 hours of exposure and response prevention treatment with a trained psychologist over 2 weeks.[3] To assess maintenance of combined ketamine and CBT effects, patients were followed for an additional 2 weeks. At baseline, 20, 90, 110, and 230 minutes after infusion, patients rated

their obsessional severity using the OCD visual analog scale.[8] At baseline and weekly for 4 weeks postketamine, an independent evaluator, blind to the study design, evaluated the patient's OCD severity using the YBOCS (primary outcome measure). Treatment response was defined a priori as 35% or greater YBOCS reduction at week 2.[8]

Of the 10 participants, 9 completed the infusion. Most participants were of European ancestry (n = 7); 2 were of African ancestry, and all but 1 described themselves as “non-Hispanic.” Genetic analyses showed 6 had Val/Val polymorphism, and 3 carried 1 or both Met substitutions (Table 1). Baseline YBOCS scores were similar in Met carriers (median, 33; range, 28–34) and Met noncarriers (median, 28; range, 21–35). Of 9 participants, 8 reported a rapid reduction in obsessive severity, as measured by the OCD visual analog scale, on the day of infusion. Brain-derived neurotrophic factor variation was not significantly associated with ketamine response on the infusion day. Two weeks after infusion, only 1 (33%) of 3 Met carriers was a responder, compared with 4 (67%) of 6 Met noncarriers (Table 1). One month after infusion (after a 2-week follow-up period), 3 (50%) of 6 Met noncarriers were responders, versus none of the Met carriers.

DISCUSSION

In this first study examining the association between the BDNF Val66Met SNP and treatment response to ketamine and CBT in OCD, there were two main findings: (1) BDNF variation was not associated with acute ketamine response on the infusion day; (2) BDNF variation was associated with differential response rate to subsequent brief, two-week, exposure-based CBT. The first finding contrasts with a study of major depression reporting enhanced antidepressant effects in Met noncarriers compared with Met carriers.[9] This contrast suggests that BDNF plays a different role in OCD. Our study's second result is consistent with the report of Fullana et al[10] that BDNF variation was associated with OCD response to 20 weekly sessions of exposure-based CBT (36% response rate in Met carriers; 60% in Met allele noncarriers), suggesting BDNF-mediated extinction learning mechanisms influence exposure-based OCD outcomes. Of note, no Met carrier (vs 50% of Met noncarriers) maintained a treatment gain in the study's follow-up period. Together, these findings also suggest that ketamine may provide only short-term relief to individuals with BDNF-mediated extinction learning deficits that impair their response to exposure-based CBT. In parallel, exposure-based CBT may maintain gains in individuals with intact BDNF-mediated extinction learning. Our study's limitations include its open-label trial design, small sample size, and lack of randomization. Clinical predictors of ketamine response have been reported in studies of major depression[11]; small sample size impacted our ability to examine clinical predictors of ketamine's effects in OCD in this pilot study. In this sample of convenience, we cannot rule out the possibility that ketamine carryover effects influenced the results of postinfusion exposure-based CBT. If replicated, however, our BDNF allele genotyping may help guide personalization of treatment for extinction-based learning.

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TABLE 1.

Obsessive-Compulsive Disorder Severity Over 4 weeks (N = 9)

				Ketamine	10 Hours of CBT				Follow-Up			
Participant	**Age**	**BDNF Genotype***	**Baseline YBOCS**	**↓**	**Week 1 YBOCS**	**% Change**	**Week 2 YBOCS**	**% Change**	**Week 3 YBOCS**	**% Change**	**Week 4 YBOCS**	**% Change**
1	55	Val/Val	27		4	**85.2**†	3	**88.9**†	2	**92.6**†	3	**88.9**†
2	25	Val/Val	29		16	**44.8**†	14	**51.7**†	15	**48.3**†	18	**37.9**†
3	39	Val/Val	27		18	33.3	16	**40.7**†	17	**37**†	17	**37**†
4	33	Val/Val	35		30	14.3	34	2.9	33	5.7	33	5.7
5	36	Val/Val	21		18	14.3	13	**38.1**†	19	9.5	21	0
6	20	Val/Val	30		15	**50.0**†	22	26.7	29	3.3	31	−3.3
7	32	Met/Met	33		19	**42.4**†	19	**42.4**†	23	30.3	22	33.3
8	40	Met/Met	34		24	29.4	24	29.4	28	17.6	30	11.8
9‡	32	Met/Val	28		34	−21.4	—	—	—	—	—	—

*Val66Met haplotype in the BDNF gene.

†Responders (in bold type) with at least 35% change from baseline.

‡Because of increased OCD symptoms, participant did not complete 10 hours of CBT.

Met indicates methionine; Val, valine.

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