THE EFFECTS OF BMI AND BDNF GENOTYPE ON PREFRONTAL CORTEX MORPHOLOGY

*E. L. BROWNING, J. PRICE, S. SHOLLENBARGER, J. WIESER, J. STRONG, K. M. LISDAHL
Department of Psychology, University of Wisconsin--Milwaukee, WI

SFN 2013: 617.07/F45

INTRODUCTION

Obesity is increasingly common in adolescents—17.4% of adolescents are considered obese [1]. Obese adolescents display gray matter losses throughout the brain [2],[3]. In a longitudinal study, adolescents with trend-level reductions in gray matter volumes in the superior and middle frontal gyri show increases in BMI at a 1-year follow-up [3]. Obese adults also display volumetric loss of gray matter in the frontal cortices and metabolic abnormalities in the prefrontal cortex [4].

BDNF (brain-derived neurotrophic factor) plays a role in energy homeostasis (for reviews, see [5],[6]). Central administration of BDNF causes appetite suppression and weight loss [7]–[11]. BDNF-conditional knockout mice display an obese phenotype with 80%-150% increase in body weight [12]. Haplo insuffiency for BDNF results in increased appetite and obesity [11], [13], [14]. A point mutation at residue 66 (Val66Met) of the *BDNF* gene causes secretory deficits [15], [16], which have been shown to effect the morphology of the PFC. Pezawas et al showed adult Met66 carriers have decreased bilateral PFC volume [17]. Adult Chinese Met66 homozygotes display decreased cortical thickness in the frontal cortex, including the OFC [18].

BMI has been shown to modify impulsivity and response inhibition in adolescents. In a study of adolescents between 12-17 years of age, increased BMI predicts levels of positive and negative urgency. BMI also negatively predicted cognitive inhibition in youth [19-20]. Obese adolescents (17.5 +/- 1.6 years) scored poorly on the total Stroop color-word score and had lower orbitofrontal cortex volume compared to lean adolescents [2].

HYPOTHESES

1. *BDNF* Met66 carriers will have decreased PFC volume and increased BMI compared to Val66 carriers
2. Brain abnormalities in *BDNF* Met66 carriers will be associated with poorer inhibitory control [20].

METHODS

- 41 healthy control subjects recruited from the community were selected from parent imaging genetics addiction study. Participants were screened by phone for eligibility. Inclusion criteria: fluent English speakers, 18-25 years old, usable MRI data. Exclusion: any neurologic conditions or major medical conditions; prenatal drug exposure; Axis I disorders including mood, anxiety and psychotic disorders; MRI contraindications; >50 past year MJ uses; >10 past year ecstasy uses; >25 past year other drug uses; <18 BMI.
- Participants underwent biological testing and DNA collection; heights and weights were measured (calculate BMI); were administered a psychological battery that included the Beck Depression Inventory II, WRAT Vocabulary Test (IQ estimate), and D-KEFS Color-Word Task; anatomical MRI scan collected on 4T Varian scanner.
- Freesurfer 5.3.1 was used to segment the PFC. Preprocessing stream included: normalization, registration to atlas, automated segmentation based on gyral landmarks, manual editing and quality checks were completed by JP. Final ROIs: superior PFC, the medial and lateral orbitofrontal PFC, and dorsolateral PFC.
- Multiple regressions controlling for past year alcohol use and gender were run to determine independent and interactive effects of BDNF genotype and BMI on PFC volumes (SPSS v20).

DEMOGRAPHICS

Average/% (SD) Demographics By Group				
	BMI < 25 (N=29)	BMI > 25 (N=12)	*BDNF* Val (N=27)	*BDNF* Met (N = 14)
Ethnicity (Caucasian)	69%	58%	63%	71%
Gender (Female)	55%	42%	48%	57%
Age	21.10 (2.30)	21.25 (2.26)	21.37 (2.15)	20.71 (2.49)
BDI-II	4.07 (3.85)	4.92 (4.40)	4.44 (3.53)	4.07 (4.87)
WRAT-4 Reading Score (Age Scaled)	104.03 (10.57)	101.92 (15.21)	103.74 (14.35)	102.79 (5.17)
Continin Level	1.54 (2.19)	1.67 (.72)	1.89 (2.47)	0.92 (1.553)
Education (Years)	13.96 (1.80)	13.92 (1.78)	14.1 (1.63)	13.64 (2.06)
BMI	N/A	N/A	24.91 (6.28)	23.16 (3.29)

Table 1: Demographic information between groups (high or average BMI and BDNF allele). There were no significant differences between groups.

Drug Usage Between Groups		
	BMI Group	BDNF Allele
Past-Year Alcohol Usage	ns	0.07
Lifetime Alcohol Usage	ns	0.09
Lifetime Nicotine Usage	ns	ns
Lifetime Marijuana Usage	ns	ns
Lifetime Other Drug Usage	ns	ns

Table 2: Drug usage between groups (high or average BMI and Val or Met BDNF allele). Alcohol usage trends toward significance, so past year alcohol usage was added to the regression.

RESULTS

- Significant BMI**BDNF* interaction in predicting dorsolateral prefrontal cortex (dlPFC) volume (β=0.381, p = 0.047). In Met carriers, greater BMI associated with larger dlPFC volume. See Figure 2.
- BMI**BDNF* marginal interaction in total PFC volume (β=0.299, p = 0.129). See Figure 3.
- Met allele carrier status: increased dlPFC volume correlated with poorer D-KEFs Color World Inhibition performance (p = .019). Val carriers did not demonstrate a significant relationship.

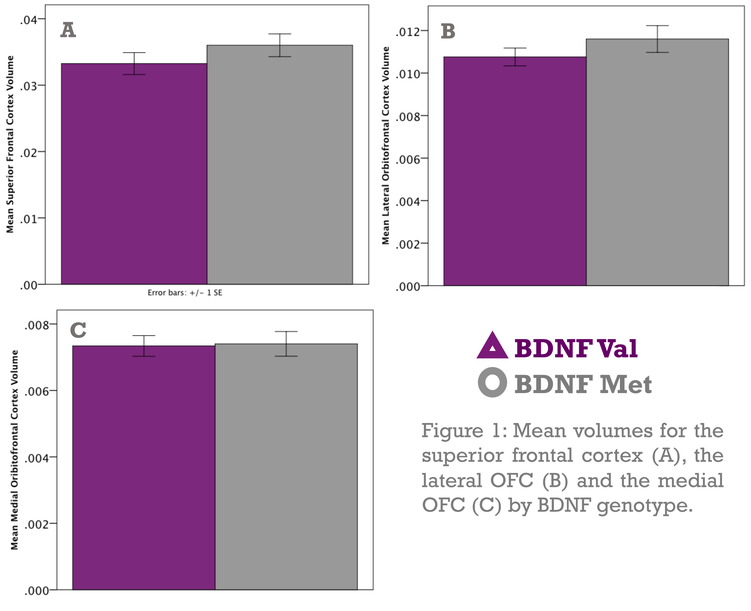
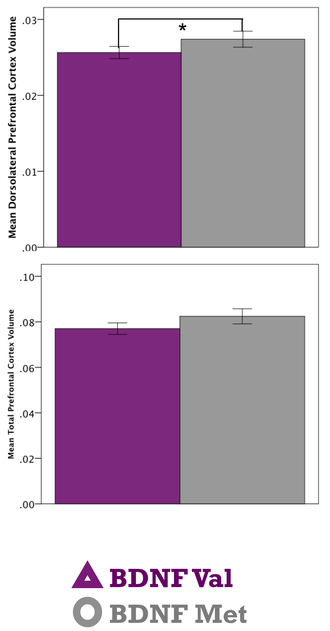


Figure 1: Mean volumes for the superior frontal cortex (A), the lateral OFC (B) and the medial OFC (C) by BDNF genotype.



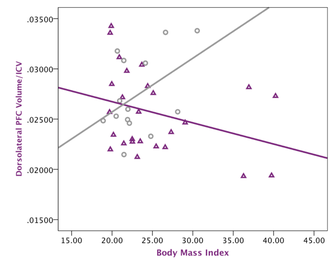


Figure 2: Mean dlPFC volume by *BDNF* genotype (left) and interaction (right). Met allele carriers are driving the interaction.

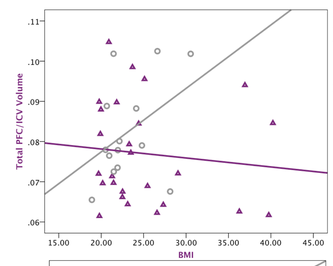


Figure 3: Mean PFC volume by *BDNF* genotype (left) and interaction (right).

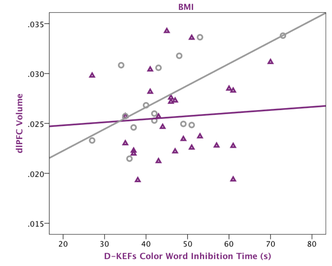


Figure 4: *BDNF* Met carriers perform worse compared to Val carriers on a Color Word Inhibition task; worse performance was correlated with larger dlPFC volume in Met carriers.

DISCUSSION

- *BDNF* Met carriers displayed larger volumes in the dlPFC.
- In Met carriers, increasing BMI was associated with larger dlPFC.
- In Met carriers, larger dlPFC was associated with poorer performance on the D-KEFs Color Word Inhibition task
- In Met carriers with overweight BMI, larger volumes in the dlPFC may represent immature development and delayed pruning.
- Consistent with previous work in healthy adolescents and emerging adults with higher BMIs performed worse on inhibitory tasks [20].
- Further, this confirms that individuals with certain genotypes and high BMI may be at greatest risk for negative cognitive effects.
- Significant public health implications; confirms need for prevention and treatment of obesity in youth.

Funding: NIDA/NIH 3R01DA030354; 1R03 DA027457 (PI: Lisdahl)

REFERENCES

[1]C. L. Ogden, M. D. Carroll, and K. M. Flegal, "High Body Mass Index for Age Among US Children and Adolescents, 2003-2006," *JAMA J. Am. Med. Assoc.*, vol. 299, no. 20, pp. 2401–2405, 2008.

[2]L. Maayan, C. Hoogendoorn, V. Sweat, and A. Convit, "Disinhibited Eating in Obese Adolescents Is Associated With Orbitofrontal Volume Reductions and Executive Dysfunction," *Obesity*, vol. 19, no. 7, pp. 1382–1387, 2011.

[3]S. Yokum, J. Ng, and E. Stice, "Relation of regional gray and white matter volumes to current BMI and future increases in BMI: a prospective MRI study," *Int J Obes*, 2011.

[4]S. Gazdzinski, J. Kornak, M. W. Weiner, and D. J. Meyerhoff, "Body mass index and magnetic resonance markers of brain integrity in adults," *Ann. Neurol.*, vol. 63, no. 5, pp. 652–657, 2008.

[5]E. E. Noble, C. Billington, C. M. Kotz, and C. Wang, "The lighter side of BDNF," *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, vol. 300, no. 5, pp. R1053–69, May 2011.

[6]J. Cordeira and M. Rios, "Weighing in the role of BDNF in the central control of eating behavior," *Mol. Neurobiol.*, vol. 44, no. 3, pp. 441–8, Dec. 2011.

[7]M. A. Pelleymounter, M. J. Cullen, and C. L. Wellman, "Characteristics of BDNF-induced weight loss," *Exp. Neurol.*, vol. 131, no. 2, pp. 229–238, Feb. 1995.

[8]C. Wang, R. J. Godar, C. Billington, and C. M. Kotz, "Chronic administration of brain-derived neurotrophic factor in the hypothalamic paraventricular nucleus reverses obesity induced by high-fat diet.," *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, vol. 298, no. 5, pp. R1320–32, May 2010.

[9]C. Wang, E. Bomberg, A. Levine, C. Billington, and C. M. Kotz, "Brain-derived neurotrophic factor in the ventromedial nucleus of the hypothalamus reduces energy intake.," *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, vol. 293, no. 3, pp. R1037–45, Sep. 2007.

[10]C. Wang, E. Bomberg, C. Billington, A. Levine, and C. M. Kotz, "Brain-derived neurotrophic factor in the hypothalamic paraventricular nucleus reduces energy intake.," *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, vol. 293, no. 3, pp. R1003–12, Sep. 2007.

[11]S. G. Kernie, D. J. Liebl, and L. F. Parada, "BDNF regulates eating behavior and locomotor activity in mice.," *EMBO J.*, vol. 19, no. 6, pp. 1290–300, Mar. 2000.

[12]M. Rios, G. Fan, C. Fekete, J. Kelly, B. Bates, R. Kuehn, R. M. Lechan, and R. Jaenisch, "Conditional deletion of brain-derived neurotrophic factor in the postnatal brain leads to obesity and hyperactivity.," *Mol. Endocrinol.*, vol. 15, no. 10, pp. 1748–57, Oct. 2001.

[13]J. Gray, G. S. H. Yeo, J. J. Cox, J. Morton, A. R. Adlam, J. M. Keogh, J. A. Yanovski, A. El Gharbawy, J. C. Han, Y. C. L. Tung, J. R. Hodges, F. L. Raymond, S. O'rahilly, and I. S. Farooqi, "Hyperphagia, severe obesity, impaired cognitive function, and hyperactivity associated with functional loss of one copy of the brain-derived neurotrophic factor (BDNF) gene.," *Diabetes*, vol. 55, no. 12, pp. 3366–71, Dec. 2006.

[14]J. C. Han, Q.-R. Liu, M. Jones, R. L. Levinn, C. M. Menzie, K. S. Jefferson-George, D. C. Adler-Wailes, E. L. Sanford, F. L. Lacbawan, G. R. Uhl, O. M. Rennert, and J. A. Yanovski, "Brain-derived neurotrophic factor and obesity in the WAGR syndrome.," *N. Engl. J. Med.*, vol. 359, no. 9, pp. 918–27, Aug. 2008.

[15]Z.-Y. Chen, A. Ieraci, H. Teng, H. Dall, C.-X. Meng, D. G. Herrera, A. Nykjaer, B. L. Hempstead, and F. S. Lee, "Sortilin controls intracellular sorting of brain-derived neurotrophic factor to the regulated secretory pathway.," *J. Neurosci.*, vol. 25, no. 26, pp. 6156–66, Jun. 2005.

[16]M. F. Egan, M. Kojima, J. H. Callicott, T. E. Goldberg, B. S. Kolachana, A. Bertolino, E. Zaitsev, B. Gold, D. Goldman, M. Dean, B. Lu, and D. R. Weinberger, "The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function.," *Cell*, vol. 112, no. 2, pp. 257–69, Jan. 2003.

[17]L. Pezawas, B. A. Verchinski, V. S. Mattay, J. H. Callicott, B. S. Kolachana, R. E. Straub, M. F. Egan, A. Meyer-Lindenberg, and D. R. Weinberger, "The Brain-Derived Neurotrophic Factor val66met Polymorphism and Variation in Human Cortical Morphology," *J. Neurosci.*, vol. 24, no. 45, pp. 10099–10102, 2004.

[18]X. Yang, P. Liu, J. Sun, G. Wang, F. Zeng, K. Yuan, J. Liu, M. Dong, K. M. von Deneen, W. Qin, and J. Tian, "Impact of Brain-Derived Neurotrophic Factor Val66Met Polymorphism on Cortical Thickness and Voxel-Based Morphometry in Healthy Chinese Young Adults," *PLoS One*, vol. 7, no. 6, p. e37777, Jun. 2012.

[19]E. Delgado-Rico, J. S. Rio-Valle, E. González-Jiménez, C. Campoy, and A. Verdejo-García, "BMI predicts emotion-driven impulsivity and cognitive inflexibility in adolescents with excess weight.," *Obesity (Silver Spring).*, vol. 20, no. 8, pp. 1604–10, Aug. 2012.

[20] Lisdahl et al, under review. *High Body Mass Index Predics Poorer Inhibitory Processing and Verbal Learning in Adolescents and Emerging Adults.*