Published in final edited form as:

Ment Health Phys Act. 2016 March ; 10: 73–77. doi:10.1016/j.mhpa.2016.01.001.

BDNF Val66Met Polymorphism as a Moderator of Exercise Enhancement of Smoking Cessation Treatment in Anxiety Vulnerable Adults

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Abstract

Background—Exercise interventions facilitate odds of quit success among high-anxiety sensitive adults smokers. We examined the dependency of these benefits on the genetic BDNF Val66Met (rs6265) polymorphism; individuals who are Met carriers have lower BDNF responses and reduced associated benefits from exercise. Accordingly, we hypothesized that the efficacy of vigorous exercise for smoking cessation would be specific to high-anxiety sensitive Val/Val carriers.

Methods—Participants were adults ($N=55$) of European ancestry who had participated in a randomized controlled trial comparing a smoking cessation program augmented with exercise vs. augmented with a wellness control treatment. In this secondary analysis, growth curve models for point-prevalence abstinence (PPA) and prolonged abstinence (PA) employed for the main outcome analyses were amended to test the moderator effects of the BDNF Val66Met polymorphism.

Results—Consistent with prediction, the advantage of exercise over control for PPA was significantly greater among high-anxiety sensitive persons with the Val/Val genotype than for

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Conflicts of Interest: The authors have declared that no competing interests exist.

those with the Val/Met genotype. This advantage did not reach statistical significance for PA. Differences in abstinence between the exercise and control interventions among low-anxiety sensitive smokers were not dependent on the BDNF Val66Met polymorphism.

Conclusions—We found that the efficacy of exercise for augmenting smoking cessation treatment is intensified among high-anxiety sensitive smokers who are Val/Val carriers. This observation is consistent with findings documenting BDNF mediation of exercise benefits and greater negative affect among smokers who are Val/Val carriers. These data encourage further evaluation of the association between the BDNF polymorphism, exercise, anxiety sensitivity, and smoking cessation.

Keywords

smoking cessation; exercise; anxiety sensitivity; biomarkers; genetics; rs6265

INTRODUCTION

Ongoing smoking cessation research and treatment efforts have begun to target individual-difference characteristics that confer greater risk for cessation failure (Warner & Burns, 2003). One such characteristic is anxiety sensitivity—the fear of anxiety and related bodily sensations—that is linked to difficulties coping with the negative experiences associated with smoking cessation (Zvolensky, Farris, Guillot, & Leventhal, 2014; Zvolensky et al., 2004, 2006). Accordingly, a treatment that reduces anxiety sensitivity and the negative affective responses to smoking cessation has the potential to be particularly valuable for high-anxiety sensitive smokers.

One intervention that offers such benefits is exercise because exercise interventions have shown to reduce anxiety sensitivity and negative affect (Asmundson et al., 2013; DeBoer, Powers, Utschig, Otto, & Smits, 2012; Smits et al., 2008; Smits, Tart, Rosenfield, & Zvolensky, 2011). We recently demonstrated that exercise can be applied successfully to smoking cessation in high-anxiety sensitive smokers (Smits et al., In Press). Specifically, high-anxiety sensitive adults who had their smoking cessation treatment augmented by a 15-week vigorous-intensity exercise program showed significantly higher point-prevalence abstinence (PPA) and prolonged abstinence (PA) rates than those receiving standard smoking cessation treatment plus a time-matched wellness education (control) intervention. These between-group differences were not evident among persons with lower anxiety sensitivity levels, suggesting that exercise efficacy for enhancing smoking cessation are specific to those who carry this particular risk for smoking cessation failure. Furthermore, the benefits of exercise mapped conceptually well onto the challenges faced by high-anxiety sensitive smokers: smokers assigned to the exercise condition reported significantly lower anxiety sensitivity, dysphoria, and anxiety during the quit week compared to those in the control condition (Smits et al., In Press).

The physiological mechanisms underlying the specific exercise benefits are not clear, in part because of the wide range of neurotransmitter and neurohormonal alternations induced by exercise (Ekkekakis, 2013). Change in brain-derived neurotrophic factor (BDNF) activity is one plausible molecular mediator given the reliable effects of exercise on BDNF activity

(Knaepen, Goekint, Heyman, & Meeusen, 2010; Szuhany, Bugatti, & Otto, 2015) and the role of restored BDNF activity in successful treatment of mood disorders (Medina, Jacquart, & Smits, 2015; Polyakova et al., 2015).

In this secondary analysis, we examined whether the BDNF Val66Met polymorphism (rs6265) predicted individual differences in the efficacy of the exercise intervention among high-anxiety sensitive smokers. The BDNF Val66Met polymorphism is a result of a G to A substitution in the coding exon VIII of the BDNF gene that leads to a substitution of amino-acid valine to methionine at position 66 of the proBDNF protein. This polymorphism, which is prevalent in 20-30% of Caucasian populations (Petryshen et al., 2010; Shimizu, Hashimoto, & Iyo, 2004), lowers activity-dependent BDNF release and associated clinical benefits (Egan et al., 2003; Hopkins, Davis, Vantieghem, Whalen, & Bucci, 2012), and therefore, may undermine the effects of interventions that exert their effects by increasing BDNF levels. Accordingly, we hypothesized that the efficacy of the exercise intervention for smoking cessation in high-anxiety sensitive adults would be stronger among Val/Val homozygous individuals relative to Met carriers.

METHODS

Participants

The parent study included 136 adult sedentary daily smokers with elevated anxiety and motivated to quit (see Smits et al., 2012) for comprehensive list of entry criteria). The genetic material collection began two years after the start of the parent study resulting in a subset of 72 participants who agreed to provide genetic data. Of these, 55 Whites (51 non-Hispanic/Latino and 4 Hispanic/Latino; 43.6% Females; Age_m=43.1[SD=12.1]) were included in the data analysis. Table 1 reports on demographic and clinical characteristics at baseline.

Interventions

A detailed description of the procedures has been provided elsewhere (Smits et al., 2012). All participants received standard treatment for smoking cessation (ST) (Fiore et al., 2008; Zvolensky, Yartz, Gregor, Gonzalez, & Bernstein, 2008), consisting of 7 weekly 60-minute sessions of cognitive behavioral therapy for smoking cessation and optional nicotine replacement therapy, which commenced at week 6 (target quit day). Participants were randomized to receive either a vigorous-intensity exercise intervention (ST+EX; 76-86% of maximum heart rate) or a wellness education control intervention (ST+CTRL; e.g., lectures on lifestyle issues). Both interventions were equivalent in time, consisting of three weekly 25-minute (exercise or wellness) sessions for 15 weeks and began at week 1.

Measures

We used the timeline follow-back procedure to assess cigarette consumption at each day following the previous assessment (Brown et al., 1998; McLeish, Zvolensky, & Bucossi, 2007). Self-reported abstinence was verified by expired carbon monoxide weekly during the intervention period and then at each assessment following the treatment-free follow-up. Abstinence at 4- and 6-months following the target quit day was additionally verified with

saliva cotinine. Positive carbon monoxide (>8ppm) or saliva cotinine verification (>10 ng/mL) (SRNT Subcommittee on Biochemical Verification, 2002) overrode self-reported abstinence. Abstinence data were considered missing if biological verification was missing (Blankers et al., 2015). We defined PPA as no smoking in the 7 days prior to an assessment, and indexed PA when participants did not report 7 or more consecutive days of smoking or smoking at least 1 cigarette over the 2 consecutive weeks prior to the assessment (Hughes et al., 2003; Smits et al., In Press). Baseline anxiety sensitivity was measured using the Anxiety Sensitivity Index-3 (ASI) (Taylor et al., 2007).

Genetic Material

Saliva samples for DNA extraction were collected using Oragene OGR-500 kits. DNA extraction (as well as genotyping and quality control) was done at the Massachusetts General Hospital Psychiatric and Neurodevelopmental Genetics Unit Core Laboratory. DNA was extracted using a Puregene protocol and quantified using PicoGreen. Genotyping of BDNF rs6265 was done using a TaqMan assay on a Roche LightCycler480. Genotyping of 40 custom designed ancestry informative markers (AIMs) was performed using the Sequenom iPLEX Gold® application and MassARRAY® system. A total of 41 markers were genotyped in 75 samples (including 2 duplicates). Quality control to determine sample and genotyping quality and to potentially remove poor SNPs and/or samples was performed in PLINK, a whole genome association analysis toolset. One sample was removed (genotyping pass rate<0.90) and duplicates were merged (concordance=1) to result in a total of 72 individuals. No SNPs were removed. To confirm the European-American subset of the sample, we used multi-dimensional scaling analysis of data from the 40 AIMs SNPs that passed quality control, in addition to self-reported race/ethnicity. The primary analysis sample of 55 individuals fell within the HapMap3 European and Gujarati Indian/Mexican ancestry clusters and reported European/Not Hispanic or Latino race/ethnicity; a subsample of 51 self-described as non-Hispanic fell within the European cluster. We completed the analysis using all 55 participants and repeated it using the subsample of 51 non-Hispanic/Latino. Because the findings did not differ between the two samples, we report on the full sample here.

DATA ANALYSES

Data were analyzed using Generalized Linear Mixed Models (GLMM). GLMM includes all participants, regardless of missing data and is the recommended intent-to-treat approach for analyzing smoking cessation trials (Hall et al., 2001). We began with the growth curve model described in the main outcome paper (Smits et al., In Press). This model employed a 3-phase piecewise growth curve model to track abstinence (separately for PPA and PA) over the 30-week study and includes attendance as a control variable. The first phase of the growth model consisted of weeks 0-6 (pre-quit treatment phase), the second phase was weeks 7-16 (post-quit/treatment phase), and the third phase was weeks 17-30 (post-treatment phase). We modeled a discontinuity in the growth curve between the first and second phase to reflect the jump in abstinence expected for the scheduled quit day. The details of the final growth curve model are reported in the main outcome paper (Smits et al., In Press). Because exercise efficacy was specific to high-anxiety sensitive participants

(Smits et al., In Press), we examined the triple interaction between treatment condition, ASI, and the BDNF Val66Met polymorphism (0=Val/Val, 1=Val/Met) to test the study hypothesis. Thus, we added the following terms to the growth curve model for abstinence: Val66Met, Val66Met x treatment condition, Val66Met x ASI, and Val66Met x treatment condition x ASI. Because the “time” variables in the growth curve model were all centered at 6-month follow-up, results for all the Val66Met terms reflect difference in abstinence at 6-month follow up.

RESULTS

Forty-two participants (76.4%) were homozygous for the Val allele and 13 (23.6%) were Met carriers (all were Val/Met). Observed genotype frequencies did not violate Hardy-Weinberg equilibrium, $X^2=0.98$, $p=.32$.

As hypothesized, there was a significant triple interaction between Val66Met, Treatment Condition, and ASI predicting abstinence, $b=.41$, $t(511)=3.53$, $p<.001$, $d=.31$ for PPA, and $b=.20$, $t(485)=2.48$, $p=.013$, $d=.23$ for PA. As can be seen in Figure 1 (which illustrates this interaction for PPA), the advantage of ST+EX over ST+CTRL was much larger for individuals with the Val/Val genotype than for those with the Val/Met genotype, but this advantage decreased for lower ASI scores (as hypothesized). For example, using the Aiken and West (1991) technique, we found that, for participants with ASI=13 or above, the advantage exercise on PPA was significantly larger for individuals with the Val/Val genotype than for those with the Val/Met genotype ($ps<.05$). However, this advantage for exercise was not significant for those with ASI=12 or lower ($ps>.061$). Although the pattern of findings for PA mirrored that observed for PPA, the between-group differences between Val/Val genotype and the Val/Met genotype in terms of the advantage of exercise did not reach significance at any ASI score that was not in the tails of the distribution for this sample.

Another way of looking at this triple interaction is to see that, for participants with the Val/Val genotype, the effects of exercise on abstinence increased as ASI increased (the advantage of ST+EX over ST+CTRL was 15% for those with ASI=10, while it was 24% for those with ASI=20). On the other hand, for participants with the Val/Met genotype, Treatment Condition had no clinical effect regardless of ASI (Treatment Condition differences were less than 1% for all values of ASI between 10 and 20).

Finally, a significant effect of Val66Met in the models indicate that participants with the Val/Val genotype had higher abstinence rates than those with the Val/Met genotype (PPA, $b=-4.97$, $t(49)=-5.99$, $p<.001$, $d=1.71$, and PA, $b=-1.17$, $t(49)=-2.36$, $p=.022$, $d=.67$).

DISCUSSION

Our findings provide initial evidence that the BDNF Val66Met polymorphism moderates the efficacy of exercise for smoking cessation among anxiety vulnerable adults. High-anxiety sensitive smokers with the Val/Val genotype assigned to the exercise intervention evidenced substantially greater PPA rates at 6-month follow-up relative to their counterparts assigned to the control condition (24 percentage points difference); the effects for PA showed a similar pattern but did not reach statistical significance. In contrast, no clinically meaningful

benefits were evident for the high-anxiety sensitive smokers with the Val/Met genotype (for both PA and PPA). As reflected in the overall trial results (Smits et al., In Press), no moderator effects were evident for the sample that did not have elevated anxiety sensitivity. These findings, coupled with those we reported previously (Smits et al., In Press), underscore the specificity of the exercise program for smoking cessation, indicating that efficacy may be strongest among those who experience greater emotional challenges at quit week (i.e., those with high anxiety sensitivity) and are more likely to have a BDNF response to exercise (i.e., Val/Val carriers)(Hopkins et al., 2012).

These initial findings raise questions with respect to possible mechanisms underlying the moderator effects observed in this analysis. Among multiple plausible candidate mediators, including BDNF availability/release, it is possible that smokers homozygous for the Val allele are in greater need for interventions that target negative affect as they attempt to quit smoking. Indeed, Jamal and associates (Jamal, Van der Does, & Penninx, 2015) found that nicotine-dependent smokers who were Val/Val carriers had greater symptoms of general anxiety and depression than Met carriers.

There are a number of study limitations. First, we are unable to confirm that the benefits of exercise in our sample are related to BDNF activity; we did not collect serum or plasma BDNF levels. Second, the observed association may be driven by another genetic variant in linkage disequilibrium with the BDNF Val66Met polymorphism, or another unmeasured third variable. Finally, the sample size was small, and consequently, effect sizes may be overestimates of the true effect. A larger sample is required to increase confidence in the findings (Duncan & Keller, 2011). Future research with larger samples may also be able to test potential differences between Val/Met and Met/Met genotypes.

Overall, the present preliminary findings suggest that the BDNF Val66Met polymorphism moderates the efficacy of exercise on smoking cessation among high-anxiety sensitive adults. If replicated, these findings would represent significant progress toward precision medicine where the selection of a smoking cessation program is tailored to the individual patient based on patient attributes (Hamburg & Collins, 2010).

Acknowledgments

Source of Funding: This study was funded by a grant from the National Institute on Drug Abuse (NIDA; R01DA027533). NIDA plays no role in approving the publications.

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HIGHLIGHTS

- Exercise facilitates the odds of smoking cessation among high-anxiety sensitive adults
- BDNF Val66Met polymorphism may moderate this effect
- Findings may represent progress toward precision medicine

Note: We plotted a limited range of ASI values since we did not want to extrapolate the estimates of PPA near the tails of the distribution of ASI for either persons with the Val/Val genotype or persons with the Met/Val genotype.

Figure 1.

PPA at 6-month Follow-up as a Function of the Interaction between BDNF Val66Met Polymorphism x Treatment Condition x Anxiety Sensitivity

Table 1

Demographic and Clinical Characteristics

	ST+EX (N=24)		ST+CTRL (N=31)		TOTAL (N=55)	
	%	N	%	N	%	(N)
Val/Met Genotype	33.3%	8	16.1%	5	23.6%	13
Sex (female)	37.5%	9	48.4%	15	43.6%	24
Education (some college)	79.2%	19	61.3%	19	69.1%	38
Employed full-time	58.3%	14	58.1%	18	58.2%	32
Married	33.3%	8	38.7%	12	36.4%	20
Ethnicity (Hispanic or Latino)	8.3%	2	6.5%	2	7.3%	4

	M	SD	M	SD	M	SD
Age	40.0	13.0	45.5	10.9	43.1	12.1
Cigarettes per day	18.0	6.7	18.0	7.8	18.0	7.2
CO reading (ppm)	15.1	8.1	16.6	7.4	16.0	7.7
FTND	4.9	1.8	6.1	1.5	5.6	1.7
ASI-3	15.6	11.5	18.6	11.6	17.3	11.5

Note: $p > 0.05$ for all between-group comparison; CO = Carbon monoxide; ppm = parts per million; ASI-3 = 18-item Anxiety Sensitivity Index – 3; FTND = Fagerström Test of Nicotine Dependence