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Original Article

Association of CREB1 (rs2253206) and BDNF (rs6265) Polymorphisms with Implementation Intentions Treatment Response in Smoking Reduction

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Abstract

Background: Previous studies have shown that implementation intentions are moderately effective in reducing smoking among smokers, but the factors determining its effectiveness are unclear. CREB1 (rs2253206) and BDNF (rs6265) polymorphisms have been proposed as the genes involved in addictive behaviors; therefore, we investigated their association with smokers' responses to implementation intentions psychotherapy.

Methods: This clinical trial was conducted on smoking male students at Tehran University and Shahid Beheshti University. The research sample was 78 smoking students who smoked at least seven cigarettes weekly. All of the participants received an implementation intentions intervention session. Their smoking rates were measured before and after the intervention, and all of them were genotyped for CREB1 (rs2253206) and BDNF (rs6265) using PCR-RFLP. The prospective-retrospective memory questionnaire (PRMQ) was used to evaluate the prospective memory (PM). Analysis of covariance (ANCOVA) and simple linear regression were used to analyze the data using SPSS version 26 at a significance level of 0.05.

Findings: The results showed that implementation intentions affect smoking reduction ($t=4.44$, $P=0.001$). Data analysis showed no relationship between these two SNPs and treatment response. Also, no association was observed between these SNPs and PM. However, regression analysis showed that PM could predict the response to treatment ($R^2=0.10$, $F=12.15$, $P=0.001$).

Conclusion: Implementation intentions can be suitable for reducing smoking. Studying the effect of genetic factors on psychotherapy in larger samples could be an effective way to individualize psychological treatments in reducing smoking, including implementation intentions.

Keywords: Smoking cessation, Genetic polymorphisms, Implementation intentions

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Introduction

Around 24% of adults worldwide smoke cigarettes.[1] A third to half of people who regularly smoke die of tobacco-related diseases approximately ten years earlier than non-smokers.[2] Smoking cessation before age 40 reduces the risk of death related to continued smoking by about 90%.[3] In 2018, nearly 55% of smokers in the United States reported attempting to stop smoking in the past year, but only 7.5% of them successfully quit.[4] Most of the time, not intending to quit smoking is not the problem of smokers, but they have difficulty achieving this goal and turning it into action.

Implementation intentions encourage smokers to quit by focusing on their efforts to convert motivation into action.[5] Implementation intentions is a cognitive psychological strategy studied to close the intention-action gap and increase goal achievement in various domains (educational, health, personal, social, and environmental).[6] According to a systematic review, participants who completed an implementation intentions intervention reduced smoking behavior at least one month later, and this effect was extremely impressive, considering the brevity of the exercise.[7]

The evidence related to the effect of psychotherapy on

the brain and the mutual influence of the environment and genes has opened a new line of research.[8] Studies show that gene-environment interactions shape people's brains. For example, a genetic polymorphism can be correlated with some traits that cause environmental changes and interact with it to determine a phenotype.[9] Therefore, it is possible to follow the explanation of the mechanisms of change in response to psychotherapy beyond the psychological level and find them at the biological level. Some studies have focused on whether the carrier of particular alleles responds better to treatment.[9] Meta-analytic evidence for the differential susceptibility model implies that treatment effects are more favorable for susceptible genotypes than non-susceptible genotypes, and carriers of these risk genotypes benefit from interventions that change the environment.[10] Identifying these genetic polymorphisms can help predict treatment response and can be used for psychotherapy prognosis in personalized medicine.[9]

Genetic and non-genetic factors influence smoking behavior (initiation, dependence, and quitting).[11] Although the genetic risk for addiction is estimated to be approximately 50%, the specific involved genes are largely unknown.[12] Genome-wide association studies (GWAS) studies have suggested the association of several gene regions with the smoking phenotype. One of the genes that have been identified in the initiation of smoking is the brain-derived neurotrophic factor (BDNF), which can change the rewarding effects of nicotine through the regulation of dopamine reward circuits. Additionally, it can play a role in the perceptual rewarding effect of nicotine by changing the drug-related memories, which ultimately increases the continuous use after the first exposure.[13]

BDNF is a neurotrophin crucial for regulating protein synthesis, synaptic plasticity, and learning. A single nucleotide polymorphism in the gene encoding BDNF in humans leads to a functional variant at codon 66 with the substitution of the amino acid valine (Val) with methionine (Met).[14] Genetic differences in BDNF have been shown in smoker and non-smoker patients with schizophrenia,[15] and the association between BDNF allelic variation and nicotine dependence in male smokers has been reported.[16] Genetic variations in BDNF increase the probability of becoming a smoker and the risk of death among smokers.[17] Smits et al reported that BDNF Val66Met polymorphism moderates the effectiveness of exercise on smoking cessation among anxiety-vulnerable adults,[18] and this polymorphism is related to smoking cessation.[19] BDNF explains the worse behavioral outcomes in some smokers, and Val66Val carriers may benefit more from smoking cessation regarding their mental health.[20] Significant associations of the Val66Met genotype with central processing, narrative processing, and perceived effectiveness of public anti-smoking advertisements and quit intentions have been reported.[21] BDNF is also involved in learning and memory and may play a role in the effect of psychotherapy, which include changes in cognition and behaviors.[22]

In a systematic review, Chen et al showed that implementation intentions intervention positively affects prospective memory (PM) performance.[23] Implementation intentions facilitate PM in tasks without salient cues and require self-initiation.[24] Chen et al argue that implementation intentions are a PM-encoding strategy. Implementation intentions specify the exact PM cues and ask people to perform tasks so that the PM task is coded more deeply and completed better.[23]

The effect of CREB1 gene polymorphism (rs2253206) on PM has been studied, and the results have shown that the single nucleotide polymorphism of rs2253206 in the CREB1 gene locus is associated with PM in healthy individuals.[25] The CREB1 protein is coded by the CREB1 gene, which is located on chromosome 2.[26]

In addition to cognition and memory, the CREB protein plays an important role in various aspects of addiction, such as neuroplasticity related to addiction.[12] CREB is essential for long-term adaptations in substance abusers.[27] CREB activity seems to be necessary for the creation of place preference by nicotine.[28] Disturbance in CREB seems to eliminate the cognitive effects of nicotine.[29] Polymorphisms are considered the main mediators in neuroplasticity,[30,31] and considering the importance of BDNF and CREB polymorphisms in cognition, memory, and addiction, we studied the role of genetic polymorphisms of these genes (BDNF [rs6265] and CREB [rs2253206]) on the effectiveness of the implementation intentions intervention on smoking cessation.

Methods

This clinical trial study investigated the effectiveness of implementation intentions intervention in smokers with BDNF and CREB polymorphisms from September 2018 to August 2020. The statistical population of this research was smoking male students of Tehran and Shahid Beheshti Universities of Medical Sciences and Tehran and Shahid Beheshti Universities. The sample size was determined based on power analysis (power = 0.95, $\alpha = 0.05$, $d = 0.5$) considering moderate effect size, so the calculated sample size was 45. However, considering the accessibility of participants, we recruited 78 participants to improve the sample size.

According to the World Health Organization definition, a smoker is a person who has smoked more than 100 cigarettes in their lifetime and currently smokes every day or most days.[32] The inclusion criteria for this study were consumption of at least seven cigarettes per week and age over 18 years. People who met the exclusion criteria, which included having neurologic problems, movement and visual defects, neurological disorders, including epilepsy, seizures, and tumors, psychiatric disorders based

on DSM-5, and using other psychoactive substances, were excluded from the study. A clinical psychologist screened all participants based on the inclusion and exclusion criteria. Demographic information and clinical history were taken from the subjects.

Before conducting the research, the participants filled out a consent form. The Vice-Chancellor in Research Affairs, Tehran University of Medical Sciences, Tehran, Iran (IRB code: IR.TUMS.VCR.REC.1397.764) approved the study.

The research process was conducted in three sessions for each participant. In the first session, baseline assessments and blood sampling were done. The intervention was conducted in the second session, and the post-test was performed in the third session.

Armitage's volitional help sheets, a two-column table in which 20 tempting situations were written in one column and 20 responses to deal with the temptation were written in the second column, were used for the if-then programs. The sheets were given to participants, and they were asked to determine which solution they thought was more suitable for them to quit smoking if they faced each situation (opposite column) and connect them with a line. For example, they could connect tempting smoking situations, such as "If I am tempted to smoke when things are not going well, and I am frustrated" or "If I am tempted to smoke when I have problems with my family," to the appropriate solution, for example, "Then I will think about something other than smoking" or "Then I will think about information and advertisements about how to quit smoking," with a line. Also, people were told that they could choose more or less appropriate situations and behavioral responses.[33]

The prospective-retrospective memory questionnaire (PRMQ) was used to measure PM. This 16-question questionnaire allows people to rate the frequency of prospective and retrospective memory slips in everyday life.[34] Subjects rated the frequency of mistakes they made on a 5-point scale. Moreover, each question is scored from 5 (very often) to 1 (never). The total score was between 16 and 80.

Subjects were genotyped for CREB1 (rs2253206) and BDNF (rs6265). Genomic DNA was extracted from blood samples using the salting-out method. The rs2253206 and rs6265 variants were determined by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) analysis (Table 1).

A paired *t* test was used to determine the intervention's effect on cigarette consumption between the pre-test and post-test. The ANCOVA method was used to determine the difference in response to treatment in different genetic groups. A simple linear regression analysis was used to investigate the relationship between PM and response to treatment.

Results

The paired-samples *t* test was used to investigate the difference in the number of cigarettes consumed before and after the intervention.

Figure 1 shows that the implementation intentions intervention reduced the number of cigarettes consumed in the post-test compared to the pre-test.

The correlation of consumption pre- and post-test was statistically significant ($r=0.841$, $P=0.001$). The paired-sample *t* test with a value of $t=4.44$ and statistical significance of $P=0.001$ showed that the implementation intentions intervention reduced the number of cigarettes consumed post-test compared to the pre-test.

Table 2 shows the average and standard deviation of the number of cigarettes consumed before and after the intervention in CREB genotypes.

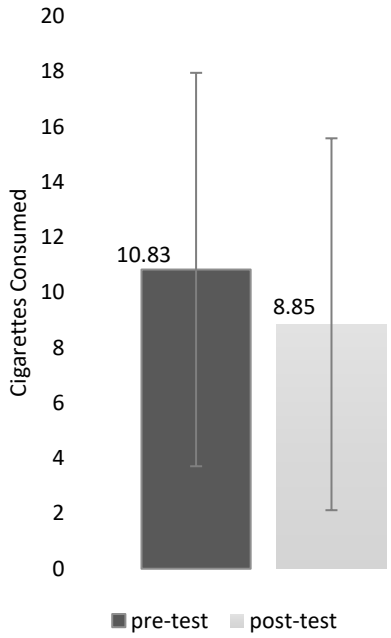

Figure 1. Cigarettes consumed pre- and post-test

Table 1. Primers and digestion protocol

SNP	Primer's sequence (5′′→3′′)	Annealing temperature	Enzyme, Cat. No.	Restriction fragment (bp)	Digestion condition
CREB1 (rs2253206)	F: TACCTGCACAATTACATGGAC R: CTTCAGGGCATTTACACATGC	60 °C	MseI, ER0981	AA:74,69 AG:143,74,69 GG:143	65 °C Incubation, 2 hours
BDNF (rs6265)	F: TACTGAGCATCACCCTGGAC R: AACATCCGAGGACAAGGTGG	63 °C	Pmac1, ER0311	CC:123,97 CT:220,123,97 TT:220	37 °C Incubation 1 hour

Levene's test was used to check the statistical assumption of homogeneity of variances in the pre-test and post-test. The results indicate that the abovementioned assumption is established: F (2,75) = 0.132, $P = 0.877$.

According to the ANCOVA results in Table 3, there is no significant difference in smoking reduction between the groups of CREB genotypes in the pre- and post-test: F (2,74) = 0.15, $P = 0.861$.

Comparison of the effect of the implementation intentions intervention on BDNF genotypes

Table 4 shows the average and standard deviation of the number of cigarettes consumed before and after the intervention in BDNF genotype groups.

Levene's test F (2,75) = 1.25, $P = 0.292$ showed homogeneity of the pre-test and post-test variances.

According to the ANCOVA results in Table 5, there is no significant difference in smoking reduction between the groups of BDNF genotypes in the pre- and post-test: F (2, 74) = 0.31, $P = 0.731$.

PM and smoking reduction after intervention

Simple linear regression was conducted to ascertain how much the PM scores can predict the difference between pre- and post-test cigarette consumption. A positive correlation was found between them ($r = 0.321$), and the regression model predicted 10% of the variance. The model fit the data well (F = 12.15, $P < 0.001$).

Do people with different CREB and BDNF genotypes differ in PM?

The results of one-way ANOVA revealed no differences in PM scores between CREB (F (2,75) = 1.22, $P = 0.301$) and BDNF (F (2,75) = 0.48, $P = 0.623$) genotypes (Table 6).

Discussion

Implementation intentions are a goal-setting technique in which people commit to performing a specific behavior in a particular situation.[7] This study aimed to investigate the effectiveness of implementation intentions in CREB1 (rs2253206) and BDNF (rs6265) polymorphisms in reducing smoking. We showed that the strategy of implementation intentions can reduce smoking, which was in line with previous studies in this area.[35-40]

One of the mechanisms proposed for the effectiveness of implementation intentions is that forming an if-then plan automates the goal effort by transferring information processing from top-down to bottom-up.[41] The automation of responses with the formation of implementation intentions[42-44] makes implementation intentions need less self-regulation.[45] There is evidence that the effects of greater cue accessibility and cue-response association on self-regulation can explain the effects of implementation intentions on behavior change.[46] In previous studies, having a strong motivation to achieve the goal could play a role in the effectiveness of implementation intentions.[36,47]

Table 2. Cigarettes consumed in CREB genotypes

N	Standard deviation		Mean		CREB
	Post-test	Pre-test	Post-test	Pre-test	
11	6.69	5.57	8.18	9.09	AA
41	6.52	7.02	8.90	11.14	AG
26	7.32	8.02	9.07	10.73	GG
78	6.73	7.12	8.85	10.83	Total

Table 3. Results for ANCOVA in CREB genotypes

Source	Type III sum of squares	df	Mean square	F	*P* value
Corrected model	2479.11	3	826.37	60.17	0.001
Intercept	1.71	1	1.71	0.12	0.725
Pre-test	2472.76	1	2472.76	180.04	0.001
CREB	4.10	2	2.05	0.15	0.861
Error	1016.33	74	13.73		
Total	9617	78			
Corrected total	3495.45	77			

Table 4. Cigarettes consumed in BDNF genotypes

N	Standard deviation		Mean		BDNF
	Post-test	Pre-test	Post-test	Pre-test	
53	6.60	7	8.64	10.81	CC
24	7.28	7.68	9.29	10.92	CT
1			10	10	TT
78	6.73	7.12	8.86	10.83	Total

Table 5. Results for ANCOVA in BDNF genotypes

Source	Type III Sum of Squares	df	Mean square	F	*P* value
Corrected model	2483.60	3	827.86	60.54	0.001
intercept	5.484	1	5.48	0.40	0.529
Pre-test	2475.30	1	2475.30	181.02	0.000
BDNF	8.59	52	4.29	0.31	0.731
Error	1011.84	74	13.67		
Total	9617.00	78			
Corrected total	3495.44	77			

Table 6. PM in different CREB and BDNF genotypes

	N	Mean	Standard deviation
CREB			
AA	11	23.63	5.76
AG	41	21.85	5.63
GG	26	20.46	6.02
BDNF			
CC	53	21.75	5.84
CT	24	21.62	5.83
TT	1	16	

In this study, the students were intent on ceasing smoking, and one of the influential factors in the effectiveness of the implementation intentions in this study could be the readiness of the students to quit smoking. Another effective factor in quitting smoking is the characteristics of people, which can be psychological or genetic.

The regression analysis showed that PM could predict smoking reduction in the post-test. PM links the sequence of complex goal-oriented behaviors and enables people to carry out their plans and desires meaningfully and at the right time.[48] In this study, people with better memory were more successful in implementing intentions to reduce smoking, which was expected due to the function of PM in performing planned actions in the future. Environmental events affect our ability to remember an action. Although genetic influences on PM have been proven, how genetic factors influence PM ability has not yet been determined.[49]

In this study, we looked at the effect of people's genotypes on intervention outcomes, and no significant difference was observed in the number of cigarettes consumed among the genetic groups after the intervention. Also, in our study, no significant relationship was observed between PM and CREB, which was inconsistent with the study of Avgan et al. The same was true for the non-relationship between PM and BDNF, which could be due to the small number of samples and the heterogeneity of our study population. Studies in the field of relationships between genetic diversity and psychotherapies are limited because this is a new line of research. These few studies are limited to specific genes such as BDNF and COMT. According to our search in related databases such as Scopus, PubMed, ScienceDirect, and Web of Science, to this date, our research is one of the first studies on the topic.

This study was one of the first to investigate the effect of BDNF and CREB genotypes in reducing smoking using implementation intentions. However, several studies have investigated the relationship between BDNF and the effects of psychological therapies, primarily related to cognitive behavioral therapies.[50,53] In some studies, a relationship has been found between BDNF and response to psychotherapy.[21,50-52] In some studies,[22,53,54] the relationship between BDNF polymorphism and response to psychological treatment was not observed. Implementation intentions are a cognitive strategy, and considering the significance of genetics on other psychotherapies, such as cognitive behavioral therapy, it seems necessary to investigate the relationship between genetics and implementation intentions.

Different explanations can be given for the contradictory results of studies in genetics and psychotherapies. First, most of these studies have been conducted with small sample sizes. Next, the difference in the study population and race can affect the results. The third reason can be the heterogeneity of the treatments; the treatments in the studies are usually different in terms of content and the number of sessions. Another explanation for this contradiction can be the individual and psychological differences between people. These differences can moderate the results of psychotherapy. For example, the exact molecular mechanisms of action in mediating psychotherapy results have not yet been determined, and many questions remain open.[55] Studies have identified various issues based on the relationship between psychotherapy and epigenetics: some have assessed that epigenetic modifications occur after psychotherapy, and some studies have examined epigenetic changes before the conduction of therapy. Various aspects need to be redefined and limitations overcome, such as increasing the sample size, homogenizing phenotypes and psychotherapies, including healthy controls to assess whether epigenetic changes are due to the passage of time, and controlling for confounding environmental factors such as the use of tobacco and psychiatric drugs.[9] Some interventions work better for some people than others. A long-term goal not only in the field of mental health but in all treatments is to identify a unique (individualized) treatment approach. Moderators and mediators of treatment effectiveness should be determined to achieve this goal. In the long term, various biomarkers such as genetic diversity, DNA methylation patterns, and gene expression profiles will help us make appropriate treatment choices to individualize treatment for mental health problems.[56]

Conclusion

The results of this study showed that the implementation intentions strategy could be effective in reducing smoking, but CREB1 (rs2253206) and BDNF (rs6265) polymorphisms do not affect treatment response to the implementation intentions strategy to quit smoking. Due to the lack of studies about the relationship between genetics and the implementation intentions method, it is suggested that studies be carried out to identify genetic predictors of response to the implementation intentions strategy.

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Authors' Contribution

Conceptualization: Neda Yadegari, Ali Yoonessi, Mehdi Tehrani-Doost.
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Supervision: Mehdi Tehrani-Doost, Ali Yoonessi, Sareh Asadi.
Writing–original draft: Neda Yadegari, Mehdi Tehrani-Doost, Sareh Asadi.
Writing–review & editing: Neda Yadegari, Mehdi Tehrani-Doost, Sareh Asadi, Ali Yoonessi, Reza Majdzadeh.

Competing Interests
There was no conflict of interest.

Ethical Approval
The Vice-Chancellor in Research Affairs, Tehran University of Medical Sciences (IRB code: IR.TUMS.VCR.REC.1397.764), approved the study, and the participants filled out the consent form before conducting the research.

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