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Individual differences in the processing of smoking-cessation video messages: An imaging genetics study

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Abstract

Studies testing the benefits of enriching smoking-cessation video ads with attention-grabbing sensory features have yielded variable results. Dopamine transporter gene (DAT1) has been implicated in attention deficits. We hypothesized that DAT1 polymorphism is partially responsible for this variability. Using functional magnetic resonance imaging, we examined brain responses to videos high or low in attention-grabbing features, indexed by “message sensation value” (MSV), in 53 smokers genotyped for DAT1. Compared to other smokers, 10/10 homozygotes showed greater neural response to High- vs. Low-MSV smoking-cessation videos in two a priori regions of interest: the right temporoparietal junction and the right ventrolateral prefrontal cortex. These regions are known to underlie stimulus-driven attentional processing. Exploratory analysis showed that the right temporoparietal response positively predicted follow-up smoking behavior indexed by urine cotinine. Our findings suggest that responses to attention-grabbing features in smoking-cessation messages is affected by the DAT1 genotype.

Keywords

Smoking; fMRI; Genetics; Message sensation value; Health communication

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.biopsycho.2017.07.019>.

Conflict of interest

The authors have declared that no competing interests exist.

1. Introduction

Public health messages delivered in video format are the mainstay of smoking-cessation campaigns that have contributed to the decline in smoking prevalence in the US (Woloshin, Schwartz, & Welch, 2008). Yet, despite these efforts, smoking remains a leading cause of mortality and morbidity worldwide, and is responsible for more than 480,000 deaths annually in the United States alone (U.S. Department of Health and Human Services, 2014). Therefore, it is imperative to identify the factors that influence audiences' cognitive processing of smoking-cessation videos (Centers for Disease Control and Prevention, 2012).

Sensory features, which attract viewer's attention through engaging visuals, edits, and music, have been hypothesized to be one such factor (D'Silva and Palmgreen, 2007; Helme, Donohew, Baier, & Zittleman, 2007; Morgan, Palmgreen, Stephenson, Hoyle, & Lorch, 2003). Message sensation value (MSV) is a validated measure that has been developed to quantify such sensory features in health promotion videos (Morgan et al., 2003). The prevailing assumption that higher MSV improves cognitive processing and effectiveness of health promotion videos has been challenged by recent neuroimaging studies, which found that videos with lower MSV were better remembered and elicited greater prefrontal and temporal response (Langleben et al., 2009; Seelig et al., 2014). These findings are consistent with predictions of the limited cognitive capacity theories. These theories suggest that although high MSV attracts viewers' attention, it also diverts cognitive resources from processing the health information content in the videos (Petty and Cacioppo, 1986; Wilson and Wolf, 2009).

While these studies question the value of utilizing high MSV as an effective communication tool, they do not address the possibility that individual differences in attention to sensory stimulation may be responsible for the lack of effectiveness of high-MSV videos at a population level (Everett and Palmgreen, 1995; Stephenson and Palmgreen, 2001). Such differences would have been of purely academic interest in the era of network television, but as media becomes more personalized, individual differences in the neurocognitive processing of health promotion videos begin to acquire real life relevance (Chua et al., 2011). Yet, experimental data on the biological basis of individual differences in the cognitive processing of health messages are very limited. Many key traits that may affect individual ability to process health messages, such as selective attention, working memory and reward sensitivity, are influenced by dopaminergic neurotransmission (Gordon, Devaney, Bean, & Vaidya, 2015). The dopamine transporter gene (DAT1) has a variable number tandem repeat (VNTR) polymorphism that modulates dopaminergic neurotransmission, with the 10-repeat (10R) and 9-repeat (9R) alleles as the most common forms (Mitchell et al., 2000). The 10R/10R homozygosity has been linked to a higher level of novelty seeking, a trait that indicates greater reactivity to novel external stimulation (Sabol et al., 1999). The 10R allele has also been consistently implicated in increased susceptibility to attention deficit disorder (ADD) (Cook et al., 1995; Gill, Daly, Heron, Hawi, & Fitzgerald, 1997; Gizer, Ficks, & Waldman, 2009; Kebir, Tabbane, Sengupta, & Joobar, 2009; Newman et al., 2014). Although it remains unclear whether this association is mediated by the dopamine or dopamine transporter levels (Yang et al., 2007), it suggests that homozygous 10R allele carriers are more likely than others to exhibit poor attentional

processing, e.g. difficulty filtering out irrelevant sensory stimuli, which is a key symptom of ADD (American Psychiatric Association, 2000). Therefore, it is possible that when exposed to public health video messages with high MSV, 10R DAT1 homozygotes would be more engaged by the attention-grabbing sensory features compared to carriers of other genotypes.

The present study sought to examine the effect of DAT1 polymorphism on the brain response to high MSV format. The value of such candidate gene approach is limited by the a priori assumptions about the relationship between the gene and the phenotype (Tabor, Risch, & Myers, 2002). However, it remains useful as the practical approach to generate initial data on the effects of individual genetic makeup on the neurocognitive processing of public health communication in a small sample (Simon et al., 2011). Such studies would help to demonstrate the relevance of genetics to the processing of public health video ads and to determine the feasibility of the larger and much more expensive genome-wide association studies. Building on the link between the 10R DAT1 allele and attentional processing deficits described above, we hypothesized that smokers with two copies of the 10R allele (10/10) would differ from smokers without the 10R homozygosity (non-10/10) in the neural response to high-MSV smoking-cessation videos. Specifically, we hypothesized that the 10/10 smokers would show greater neural response to high-MSV vs. low-MSV videos than the non-10/10 smokers in two brain regions: the right temporoparietal junction (rTPJ) and the right ventrolateral prefrontal cortex (rVLPFC). These regions form the strongly right lateralized “ventral attention network” that underlies bottom-up, stimulus-driven attentional processing (Corbetta and Shulman, 2002; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Petersen and Posner, 2012; Vossel, Geng, & Fink, 2014), and are thus likely to be modulated by the greater attention-grabbing sensory content in high-MSV videos. The secondary aim of the present study was to explore the contribution of the differences between 10/10 and non-10/10 smokers’ ventral attention network response during one-time exposure to smoking-cessation videos to individual variation in future smoking behavior. Smoking was indexed by subjective (self-report) (Gorber, Schofield-Hurwitz, Hardt, Levasseur, & Tremblay, 2009; Perezstable, Marin, Marin, Brody, & Benowitz, 1990) and objective (urine levels of the nicotine metabolite cotinine) measures of smoking (Pokorski, Chen, & Bertholf, 1994; Wall, Johnson, Jacob, & Benowitz, 1988), immediately before and approximately one month after the one-time exposure to 16 smoking-cessation videos.

2. Materials and methods

2.1. Participants

Seventy-four non-treatment-seeking adult daily smokers participated in the study. Eight participants were excluded due to excessive (> 1 voxel) head motion during the MRI scan and 15 participants declined to be genotyped, leaving 53 participants (23 female; 3 lefthanded) who passed MRI quality control and were genotyped. Participants reported their racial-ethnic characteristics as follows: 28 White, 19 African American, 4 Asian, and 2 Hispanic. Their ages ranged between 18 and 49 years ($M \pm SE = 31.34 \pm 1.33$), with 14.16 ± 0.26 years of education. All participants gave written informed consent to participate in the protocol approved by the University of Pennsylvania Institutional Review Board. Exclusion criteria were (1) presence of any DSM-IV-TR Axis 1 psychiatric disorder except

tobacco use disorder (American Psychiatric Association, 2000); (2) urine drug screen positive for illicit opioids, benzodiazepines, cannabinoids, cocaine, or methamphetamine; (3) baseline urinary cotinine levels <50 ng/ml (SRNT Subcommittee on Biochemical Verification, 2002); (4) presence of medical or neurological disorder or treatment that may affect the cerebrovascular system; and (5) safety-related contraindications for MRI scanning.

2.2. Task

The video-viewing task is described in the Supplementary materials and in Wang et al. (2013). Each participant viewed eight smoking-cessation videos with Low MSV and eight with High MSV in a random order, separated by a 16 s rest period (gray cross-hair on a homogenous black background). A 16 s rest period was also presented at the beginning of the task. Each video was 30 s long and presented only once.

2.3. Genotyping

Genomic DNA was extracted from anti-coagulated venous blood samples using a standard salting out method (Lahiri and Nurnberger, 1991). Genotyping of the DAT1 40 bp repeat polymorphism (rs28363170) was performed as previously described (Franklin et al., 2009; Vandenberg et al., 1992) (see Supplementary material). Participants were divided into two cohorts by the DAT1 genotype: 26 homozygous (two copies) for the 10-repeat allele, and 27 with one or no 10R alleles (21 with 10R/9R, 2 with 9R/8R, and 1 each with 10R/8R, 9R/9R, and 3R/3R).

2.4. Procedure

The study included a phone screening, baseline assessment, fMRI session, and a follow-up session 1 month later. Participants were asked to avoid nicotine-replacement products throughout the study and to report any use of such products. At the baseline session, participants were evaluated for eligibility, demographics, and handedness (Oldfield, 1971). One hour before the fMRI session, participants provided urine samples for baseline cotinine levels, reported the average number of cigarettes smoked per day in the past 30 days, and completed the Fagerstrom Test of Nicotine Dependence (FTND) (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) and other behavioral assessments (see Supplementary material). Approximately 30–45 min before the fMRI session, participants were given an opportunity to smoke one of their own cigarettes outdoors under observation. This minimized individual differences in craving for cigarettes during fMRI session, and avoided this potential confound to the brain response to smoking-cessation videos. All participants took the opportunity to smoke. Before the video task began, participants were instructed to attend to the videos. At the follow-up session approximately 30 days later ($M \pm SE = 32.08 \pm 2.10$ d), urine samples for cotinine level were again obtained. Participants were debriefed about the cotinine assay and the study hypotheses only after completion of all assessments.

2.5. MRI data acquisition

MRI imaging was performed using Siemens Tim Trio 3T (Erlangen) system and a 32-channel receive-only head coil. Blood oxygenation level-dependent (BOLD) fMRI was performed, using a whole-brain, single-shot gradient-echo echo-planar sequence with the

following parameters: TR/TE = 2000/30 ms, FOV = 220 mm, matrix = 64×64 , slice thickness/gap = 3.4/0 mm, 32 slices, effective voxel resolution of $3.4 \times 3.4 \times 3.4$ mm. After BOLD fMRI, 5-min MPRAGE T1-weighted images were acquired with the following parameters: TR/TE = 1630/3.87 ms, FOV = 250 mm, matrix = 256×192 , effective voxel resolution of $1 \times 1 \times 1$ mm. An oblique acquisition, oriented along the anterior commissure–posterior commissure line, allowed coverage of the entire brain with the exception of the lower cerebellum.

2.6. Functional imaging data analysis

Functional imaging data were analyzed using SPM 8 (Wellcome Trust Centre for Neuroimaging, London, UK). Images were adjusted for slice timing, realigned to the first scan to correct for head motion, normalized into stereotactic Montreal Neurological Institute (MNI) space with 3-mm cubic voxels, and spatially smoothed by a Gaussian filter with full-width/half-maximum parameter (FWHM) set to 8 mm. Voxelwise individual-level statistical analyses were performed by modeling High-MSV and Low-MSV videos using a canonical hemodynamic response function. Six rigid body motion parameters were included as covariates, and the rest periods were treated as the baseline. The effects of MSV were tested by contrasting High-MSV videos with Low-MSV videos. To test the difference in MSV effect between 10/10 and non-10/10 participants, contrast images were subjected to independent-sample *t*-tests to examine the effect of DAT1 genotype (10/10 vs. non-10/10). The MSV effect across all participants was examined by one-sample *t*-test and is reported in the Supplementary material as a replication of a previous study (Wang et al., 2013).

Two key regions of the ventral attention network, the right temporoparietal junction (rTPJ) and the right ventrolateral prefrontal cortex (rVLPFC), were tested as a priori regions of interest (ROIs). Based on a previous meta-analysis (Fox et al., 2006), the rTPJ and rVLPFC ROIs were defined as 6-radius spheres centered at $x/y/z = 59/-47/22$ and $x/y/z = 41/21/-6$ (MNI coordinates converted from Talairach space (Lancaster et al., 2007)). We also conducted a preliminary wholebrain search for the 10/10 vs non-10/10 group differences in other brain regions. We used a common procedure that included a 2000-iteration Monte-Carlo simulation that determined the combined “voxellevel $p < 0.005$ ” and “cluster size > 52 ” thresholds required for a whole-brain corrected $p < 0.05$. Similar threshold has been shown to produce a balance in Type I and Type II errors (Lieberman and Cunningham, 2009). Contrast values of parameter estimates were extracted from significant clusters using MarsBaR 0.42 (<http://marsbar.sourceforge.net>) for post hoc correlation and mediation analyses.

2.7. Predictability analysis

We used the leave-one-out cross-validation analysis to test whether brain response could predict future smoking behavior measured by cotinine levels at the follow-up session (Hastie, Tibshirani, & Friedman, 2009). We performed a regression analysis on all except one participant, with follow-up cotinine levels (adjusted for baseline levels) as the dependent variable, and the brain response as the independent variable. The parameter estimates obtained from the regression model were then applied to the omitted participant, yielding a predicted value of his/her follow-up cotinine level. After repeating this procedure over every

participant, the inaccuracy of prediction was estimated by the mean squared error (MSE), that is, $MSE = [\sum_i (\hat{Y}_{-i} - Y_i)^2] / N$, where N is the number of participants, Y_i is the actual follow-up cotinine level for the i -th participant, and $\hat{Y}_{-i}$ is the predicted follow-up cotinine level for the i -th participant based on the regression model with all but the i -th participant. The significance of MSE was determined by a permutation test. For each of the 10,000 permutations, a random MSE (i.e. MSE_{null}) was calculated after permuting the correspondence between follow-up cotinine levels and brain response. This yielded an empirical distribution of prediction inaccuracy under the null hypothesis that there was no association between brain response and follow-up cotinine levels. The significance of the original MSE was then calculated as $\text{Prob}(MSE \leq MSE_{null})$.

2.8. Mediation analysis

To determine whether brain response to MSV in the ventral attention network mediated effects of DAT1 genotype on cotinine levels at the follow-up session, we conducted mediation analysis using the PROCESS macro for SPSS 22 (Model 4; <http://www.processmacro.org>). The significance of the indirect effect was determined by a 5000-iteration bootstrapping procedure (Preacher and Hayes, 2004, 2008). Although the direct and total effects have had less weight in recent literature, we examined them as well, to better connect with the earlier literature (Rucker, Preacher, Tormala, & Petty, 2011; Shrout and Bolger, 2002; Zhao, Lynch, & Chen, 2010). Listwise deletion was used to manage missing values. This procedure removed five 10/10 participants and eight non-10/10 participants leaving a total of 40 participants in the model. We also used multiple imputations as an alternative way to manage missing values (Allison, 2001).

3. Results

3.1. Participant characteristics

The demographic characteristics of the 10/10 cohort were: $N = 26$, 16 females; 2 left-handed; 10 Caucasian, 13 African American, 2 Asian, 1 Hispanic; aged 18–47 years (32.42 ± 1.93); with 13.75 ± 0.41 years of education. The demographic characteristics of the non-10/10 cohort were: $N = 27$, 7 female; 1 left-handed; 18 Caucasian, 6 African American, 2 Asian, 1 Hispanic; aged 19–49 years ($M \pm SE = 31.30 \pm 1.84$); with 14.56 ± 0.33 years of education. The two cohorts did not differ in handedness ($\chi^2(1) = 0.40$, $p = 0.53$), race ($\chi^2(3) = 4.85$, $p = 0.18$), age ($t(51) = -0.80$, $p = 0.43$), or years of education ($t(51) = 1.55$, $p = 0.13$). The 10/10 cohort contained significantly more female participants than the non-10/10 cohort ($\chi^2(1) = 6.84$, $p < 0.01$). Behavioral measures including urine cotinine levels, FTND scores, and self-reported cigarettes per day at baseline and at 30-day follow-up are summarized in Table 1. There was no significant main effect of time of assessment (baseline vs. follow-up) or genotype (10/10 vs. non-10/10) or interaction ($F_s < 1.16$, $p_s > 0.29$). There was a trend for positive correlation between follow-up cotinine levels and self-reported cigarettes per day, after adjusting for baseline ($r = 0.31$, $p = 0.056$).

3.2. fMRI results

Analysis of the a priori ROIs showed that, compared to the non-10/10 participants, the 10/10 participants showed greater rTPJ response to the High-MSV vs. Low-MSV smoking-

cessation videos ($M \pm SE = 0.20 \pm 0.06$ vs. 0.00 ± 0.05 ; $t(51) = 2.42$, $p < 0.02$). A trend in the same direction was found for the rVLPFC (-0.02 ± 0.05 vs. -0.19 ± 0.07 ; $t(51) = 1.92$, $p = 0.06$). Wholebrain analysis showed that, compared to the non-10/10 participants, the 10/10 participants showed greater neural response to High-MSV vs. Low-MSV videos at the left TPJ (ITPJ), rTPJ, rVLPFC, and right middle temporal gyrus (rMTG) (see Fig. 1 and Table 2). No regions showed greater MSV effect in the non-10/10 compared to 10/10 participants. These findings remained significant after controlling for race and gender (see Supplementary results).

3.3. Predictability and mediation analysis

The rTPJ response to the High-MSV vs. Low-MSV videos positively predicted follow-up urine cotinine levels adjusted for baseline levels ($r = 0.37$, $p < 0.02$) (see Fig. 2A). Leave-one-out cross-validation confirmed the predictive power of the rTPJ neural response, which produced significantly smaller MSE compared to that obtained from randomization ($p < 0.02$) (see Fig. 2B). The rVLPFC response was not correlated with cotinine levels ($r = 0.18$, $p = 0.26$). Similarly, there was no correlation between the rTPJ response and self-reported cigarettes per day ($r = 0.21$, $p = 0.18$).

Next, we tested the mediation model using DAT1 genotype as the independent variable (1 = 10/10, -1 = non-10/10), follow-up cotinine levels as the dependent variable, rTPJ response to High-MSV vs. Low-MSV videos as the mediator, and baseline cotinine levels as a covariate. There was a significant indirect effect of DAT1 genotype on follow-up cotinine levels through the rTPJ neural response (indirect effect = 146.70, bootstrap SE = 73.17, 95% bootstrap confidence interval = [36.09, 334.68], $p < 0.005$). The total and direct effects were not significant ($ps > 0.40$). Using multiple imputations (20) instead of listwise deletion produced similar results ($ps < 0.05$). These findings remained significant after controlling for race and gender (see Supplementary results). Substituting urine cotinine levels with cigarettes per day as the outcome variable yielded a similar mediation effect (indirect effect = 0.50, bootstrap SE = 0.33, 95% bootstrap confidence interval = [-0.04, 1.30], $p = 0.07$) at a trend level.

4. Discussion

We found that the DAT1 polymorphism modulated smokers' brain response to the attention-grabbing sensory features in smoking-cessation videos. Specifically, smokers with the 10/10 genotype showed greater response to the high-MSV vs. low-MSV videos in the rTPJ and the rVLPFC, whereas the non-10/10 smokers showed the opposite pattern. The rTPJ and rVLPFC comprise the ventral stream of the frontoparietal attention network and are mainly involved in bottom-up attention reorienting toward distinctive extraneous stimuli (Corbetta and Shulman, 2002; Fox et al., 2006; Petersen and Posner, 2012; Vossel et al., 2014), both visual and auditory (Downar, Crawley, Mikulis, & Davis, 2000; Kim, 2014). Hence, our findings suggest an increased bottom-up attention toward the high-MSV format for the 10/10 participants and vice versa for the non-10/10 participants. This is consistent with our hypothesis that the DAT1 polymorphism contributes to individual variability in the cognitive

processing of antismoking videos. Nevertheless, since we did not employ direct measures of attention, future studies would be required to confirm this interpretation.

The ventral attention network, however, does not simply respond to salient stimuli. Instead, it is modulated by task-relevance, such that its activity is restricted to important, target stimuli (de Fockert, Rees, Frith, & Lavie, 2004; Indovina and Macaluso, 2007) or distracters that share features with the target (Serences et al., 2005). This phenomenon implies a filtering mechanism of the ventral attention network (especially the rTPJ) that prevents irrelevant information from being attended to. Failure to suppress the network's response to distracters may result in compromised information processing (Corbetta, Patel, & Shulman, 2008; Shulman, Astafiev, McAvoy, Davossa, & Corbetta, 2007). Therefore, in the present study, the 10/10 participants' excessive rTPJ response to the high-MSV format might have impaired their effective processing of the anti-smoking information in the videos. Since we did not measure participants' information processing efficiency directly during the task, this assumption would require confirmation through additional research. We also showed that neural activity of the rTPJ predicted urine cotinine levels approximately one month after exposure to the videos. Specifically, the rTPJ response to the high-MSV vs. low-MSV videos was positively correlated with future smoking and mediated the effect of genotype on that behavior. These findings suggest that greater rTPJ response to the high-MSV format is associated with poorer long-term behavioral responsiveness to smoking-cessation messaging. A possible explanation could be that the 10/10 individuals developed a less adaptive processing style that focused on the sensory features of the videos, and thus received less benefit from the anti-smoking information (Langleben et al., 2009; Seelig et al., 2014).

Together, our findings contribute to the existing literature in several ways. First, they extend prior studies on the mechanisms of neurocognitive processing of the high-MSV format (Langleben et al., 2009; Seelig et al., 2014; Wang et al., 2013) to genetic variability, i.e. the DAT1 polymorphism. Second, previous studies have shown that neural activity of the self-referential processing regions, such as the medial prefrontal cortex and the posterior cingulate cortex/precuneus, predict the behavioral outcomes of health communication (Chua et al., 2011; Falk, Berkman, Mann, Harrison, & Lieberman, 2010; Wang et al., 2013). Here, we expand these findings by showing that the differential engagement of the attention network (e.g. rTPJ) in response to video format is an additional outcome predictor. Third, the 10R DAT1 allele is associated with high risk for ADD (Cook et al., 1995; Gill et al., 1997; Gizer et al., 2009; Kebir et al., 2009; Newman et al., 2014), addiction (Stolf et al., 2014) and poorer outcomes of smoking-cessation treatment (Lerman et al., 1999; O'Gara et al., 2007; Stapleton, Sutherland, & O'Gara, 2007). The present study adds a neurobiological dimension to this literature by showing that 10/10 smokers may have less effective cognitive processing of smoking-cessation videos and may derive less benefit from population-level public health interventions than other smokers.

Findings for the self-reported cigarettes per day were at a trend level and in the same direction as urine cotinine. This is in agreement with prior literature suggesting that self-report is less sensitive to individual differences in response to smoking-cessation videos than urine cotinine (Gorber et al., 2009; Perezstable et al., 1990; Pokorski et al., 1994; Wall et al.,

1988). The relationship between biological and self-report measures in addiction research is often indirect, with both over- and underestimation of addiction severity depending on context (de Beaupaire et al., 2007; Devine et al., 2013). For this reason, laboratory confirmation of self-report by urine analysis is the standard of practice in substance abuse treatment. The number of cigarettes smoked per day is only a rough approximation of the amount of nicotine actually inhaled and then absorbed and metabolized, as the inhaled volume and the portion of a cigarette actually consumed varies widely within and between participants. Cotinine levels are a more reliable and objective measure of the effective amount of nicotine active in the body (Benowitz et al., 2009) and also have predictive value in cancer research (Zhu et al., 2013). Therefore, it is not surprising that the neural response to smoking-cessation videos was a better predictor of urine cotinine levels than of self-reported smoking behavior.

Our findings inform the neurocognitive mechanisms of anti-smoking communication processing among smokers with DAT1 10/10 and non-10/10 genotypes. Although using the genotype to personalize health communications (Wang et al., 2016) may not be feasible in the foreseeable future, we believe that these findings may help inform future development of anti-smoking communication strategies, so that “less responsive” smokers (in this case DAT1 10/10 homozygotes) benefit from anti-smoking ads as much as other smokers. Specifically, the reduced effectiveness of high-MSV videos in imparting health information to the 10/10 smokers suggests that it may be challenging to produce videos that would attract the 10/10 smokers’ attention without distracting them from the message content. One option is to use lower MSV videos. However, this approach may fail to attract the 10/10 smokers’ attention altogether (Morgan et al., 2003). Another option is to strengthen the ads’ content to help them survive the distraction of high MSV in this population. This could be achieved by including antismoking arguments that have been independently rated as more persuasive (Zhao, Strasser, Cappella, Lerman, & Fishbein, 2011). Previous research showed that high-MSV video messages were better remembered than low-MSV ones only when the ads’ argument strength was high (Wang et al., 2013). Although the sample size of the present study does not permit testing the three-way interaction of DAT1 genotype, MSV and argument strength, determining whether increasing argument strength could attenuate the detrimental effect of high MSV on the effectiveness of smoking-cessation videos among 10/10 smokers is a worthwhile subject of future research.

Our study comes with a number of limitations. Although we were interested in the attentional processing of the smoking-cessation videos, we did not directly measure attention during video viewing. This limited our ability to infer psychological functions from the observed brain responses. It would be interesting to address this issue by incorporating measures such as eye-tracking for each video in the future studies (Nardo, Santangelo, & Macaluso, 2011). We focused on a single polymorphism in a limited sample of smokers. However, neurocognitive endophenotypes may be largely polygenic, exhibiting additive effects from multiple genetic variants (Iacono, Vaidyanathan, Vrieze, & Malone, 2014; Vrieze et al., 2014). Other genes commonly associated with dopaminergic neurotransmission include COMT and the dopamine receptor genes DRD2 and DRD4 (Frank, Moustafa, Haughey, Curran, & Hutchison, 2007). Studies support a potential role for DRD2 and DRD4, but not COMT in attention processing (Barnett, Scoriels, & Munafo,

2008; Cheuk and Wong, 2006; Gizer et al., 2009; Sun, Yuan, Shen, Xiong, & Wu, 2014). Despite the known limitations of the single candidate gene approach, our findings set the stage for further research examining a more comprehensive set of candidate genes or genome-wide association (Tabor et al., 2002) that would provide a more complete picture of the neural and genetic effects of cessation videos on smoking (Falcone et al., 2013). Additionally, given the greater risk of Type I error with small sample sizes, our findings will need to be replicated in an independent cohort with a larger sample size. We did not include control videos (i.e. videos not promoting smoking cessation) or control subjects (i.e. non-smokers). Therefore, our findings may not be specific to smoking-cessation videos. However, even if our findings reflect viewers' capacity to process persuasive video advertising in general, their potential relevance to smoking-cessation communications remains. Future studies could evaluate the interaction between genotype and smoking status (current, former and at-risk) on both health and other messages. In addition, although our findings were unchanged after controlling for gender, it should be noted that there are substantial gender differences in the rates of response to nicotine replacement therapy (Wetter et al., 1999) and in susceptibility to antismoking communications (Toll et al., 2008). Lastly, given the liberal threshold we used for the exploratory whole-brain analysis, the neural response of the non-a priori clusters (i.e. the ITPJ and rMTG) should be interpreted with caution (Eklund, Nichols, & Knutsson, 2016).

5. Conclusions

DAT1 genotype significantly contributes to the individual variability in brain response to the level of sensory stimulation by smoking cessation videos, which in turn predicts future smoking behavior. Genetic variability should be taken into account in future studies of the brain processing of health communications. These findings may help inform future efforts in identifying message characteristics that can better reach smokers who may be less responsive to mass-media public health campaigns.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

(A) Brain regions showing greater MSV effect in the 10/10 than non-10/10 participants. (B) Contrast values of High-MSV vs. Low-MSV. ITPJ/rTPJ: left/right temporoparietal junction; rVLPFC: right ventrolateral prefrontal cortex; rMTG: right middle temporal gyrus. Error bar: standard error of mean.

Fig. 2.

(A) The rTPJ response to High-MSV vs. Low-MSV smoking-cessation videos was positively correlated with follow-up cotinine levels (adjusted for baseline). (B) Leave-one-out cross-validation showed that the rTPJ neural response was predictive of follow-up cotinine levels with significantly smaller prediction error (i.e. mean squared error of prediction, MSE) as compared to the null distribution of prediction error (MSE_{null}) obtained through 10,000 permutations (solid line: real MSE value produced by original data; dashed line: 5th percentile of the empirical MSE_{null} produced by permutation). rTPJ: right temporoparietal junction.

Table 1Summary of behavioral measures ($M \pm SE$).

	All participants	10/10	vs.	non-10/10
Baseline				
Cotinine (ng/ml)	1506.08 $\pm$ 269.21	1814.96 $\pm$ 522.87	vs.	1221.92 $\pm$ 186.88
FTND	4.43 $\pm$ 0.31	4.50 $\pm$ 0.74	vs.	4.37 $\pm$ 0.41
Cigarettes per day	14.72 $\pm$ 0.91	14.00 $\pm$ 1.16	vs.	15.41 $\pm$ 1.34
30 days after video-viewing task				
Cotinine (ng/ml)	1437.69 $\pm$ 167.54	1581.14 $\pm$ 284.86	vs.	1294.24 $\pm$ 178.54
(adjusted for baseline)	1437.69 $\pm$ 121.08	1471.15 $\pm$ 192.95	vs.	1400.71 $\pm$ 144.92
FTND	4.30 $\pm$ 0.39	4.42 $\pm$ 0.57	vs.	4.17 $\pm$ 0.53
Cigarettes per day	14.27 $\pm$ 1.12	14.09 $\pm$ 1.46	vs.	14.47 $\pm$ 1.79

FTND: Fagerstrom Test of Nicotine Dependence.

Table 2
Brain regions showing greater MSV effect in the 10/10 than non-10/10 participants.

Region	BA	Size	Z	MNI coordinates		
				x	y	z
Left temporoparietal junction	39/40	258	3.81	-60	-49	31
Right temporoparietal junction	39/40	200	3.24	48	-43	34
Right ventrolateral prefrontal cortex	47	54	3.52	27	14	-23
Right middle temporal gyrus	21	71	3.23	45	-37	-2

BA: Brodmann area; Size: number of voxels; MNI: Montreal Neurological Institute coordinate system. Z values and MNI coordinates represent the peak voxel the cluster.