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Brain Responses to Anti-Smoking Health Warnings In Youth

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Abstract

Purpose of the Review—Adolescents and young adults are a critical target for smoking prevention efforts. Health education is a key approach to these efforts, yet little is known about how adolescents and young adults process health information. One novel approach to understanding the neurobiological mechanisms of cognitive processing of public health communications is to use neuroimaging techniques to map the brain regions involved and make inferences about the neural systems engaged in the processing of health information. We reviewed recent studies that employed functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) to examine the brain responses of adolescents and young adults to anti-smoking health messages and videos.

Findings—This narrative literature review found that the medial prefrontal cortex, amygdala, and hippocampus were the brain regions most commonly engaged in response to health warnings. Developmental factors modulate the relationship between brain regions, regulated emotional reaction, and frontal regions that are responsible for decision making.

Summary—Research that integrates neurophysiology and behavior to study adolescent and young adult neurocognitive responses to health messaging is an important tool for identifying optimal methods to communicate the health hazards of smoking to this vulnerable population.

Keywords

Anti-smoking health warnings; Adolescents and young adults; Brain response; fMRI; EEG

Background

Cigarette smoking is responsible for almost half a million deaths in the USA annually, making it the leading preventable cause of death among Americans (1). According to the Center for Disease Control, on any given day, more than three thousand children and adolescents have their first cigarette, and approximately two thirds of them eventually become daily smokers (2). Youths who have not started smoking by the age of 18 are less

likely to ever become daily smokers (2, 3), suggesting that adolescence and the transition to young adulthood is a key developmental period in the prevention of smoking initiation and progression.

Adolescents and young adults exhibit, on average, greater impulsivity and more risk-taking behaviors, than older individuals. Neuroimaging studies indicate that the rapid brain maturation that occurs during adolescence and young adulthood is uneven, with rostral (anterior) parts of the cortex maturing later than the more caudal (posterior) and subcortical regions (4). The more rostral (anterior) parts of the prefrontal cortex, which mediate executive functions such as decision making, planning and response inhibition, are slower to develop than the phylogenetically older and more dorsal regions of the brain (4), such as the amygdala, which mediates rapid responses to both rewarding and threatening stimuli (5–10). This morphologically uneven development has been hypothesized to be a major contributor to the heightened susceptibility to impulsive decisions, and greater incidence of risky health behaviors during adolescence and young adulthood. In an oversimplified model, this transient maturational state creates an “imbalance” between the brain’s action and the control systems, leading to adolescents’ greater tendency toward risky actions without considering the consequences (7, 11, 12).

Today’s adolescents have higher levels of media access than prior generations. This level of access along with a biological tendency for impulsive behavior makes youths a target for sophisticated media campaigns advertising harmful products such as tobacco (3). There is evidence that adolescents’ level of exposure to smoking in the media is correlated with both the likelihood of tobacco use and intention to use tobacco (13). Although this level of media access presents an unprecedented opportunity to reach young people with health information, both positive and negative, about various risk-related behaviors, public health outreach efforts do not match the high levels of tobacco advertising. In particular, tobacco companies have taken advantage of the new media environment and are spending billions annually on advertising targeting the younger generation. In 2014 alone, the tobacco industry spent 9 billion dollars on the advertisement and promotion of cigarettes (14). In comparison, states receive an allocated amount of funding for tobacco control and prevention, and often their spending does not meet even CDC-recommended levels, much less match those of the tobacco industry (15).

Warning labels on cigarette packs is one of preventive strategies that promote public awareness of the health hazards of smoking. To improve their effectiveness, more than 100 countries worldwide have adapted graphic warning labels (GWLs), which consist of a textual warning statement and an emotionally charged image depicting the negative health consequences of smoking on cigarette packages (16). In the US, the current regulation only requires cigarette packs to carry the textual Surgeon General’s warning, which has remained unchanged since 1984. Studies suggest that the text-only labels are not effective in promoting behavioral changes (17). The 2009 Family Smoking Prevention and Tobacco Control Act (FTA) called for replace these labels with composite graphic warning labels (GWLs) that include images and textual warnings (18). However, the US Food and Drug Administration (FDA) was unable to implement the GWLs, due to concerns about their constitutionality (19). Tobacco companies successfully argued in court that the FDA-

proposed GWLs, "...were chosen not to convey information, but to evoke negative emotions and thereby discourage smoking." (20). The appeals court agreed that the FDA did not provide sufficient experimental bio-behavioral data to support their claim that the public health benefit of the GWLs they selected outweighed the potential infringement of the First Amendment (21). Although many studies argue that GWLs are more effective than the text-only warning labels (16, 17, 19, 22, 23), an overwhelming majority of these studies are based on cross-sectional surveys and other self-report measures (21). This knowledge gap is now being filled by studies using objective measures, such as neuroimaging. Such studies in adults have already shown that the emotional salience of the graphic component of the GWLs is positively correlated with their effectiveness in dampening cigarette craving and attenuating attention bias towards smoking cues (24, 25). Similar data on adolescents is scarce, although new studies are beginning to emerge.

The goal of our review is to summarize research that used neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) to study adolescent and young adult brain responses to anti-smoking health messages, such as the FDA-proposed GWLs and anti-smoking public service announcements (PSAs). Neuroimaging allows for the investigation of objective neurobiological responses that may account for variability in future behaviors in response to health messages not explained by self-reported variables (26, 27).

Methods

The literature search included papers published between January 2011 and July 2017, and focused on neuroimaging studies of health messaging only. We searched PubMed, PsycInfo, ScienceDirect, and JSTOR for keywords that included at least one word in each of three categories: [fMRI, EEG, PET, PET, SPECT, MEEG or fNIRS], [adolescents, young adults], [smoking, health messages, anti-tobacco, warning labels, neural correlates, tobacco, public service announcements, warning labels, media].

Results

We identified six studies that met our search criteria. Four used fMRI and 2 used EEG to study brain responses to health messages in adolescents or young adults (Table 1). We did not find any relevant studies that used PET, SPECT, MEEG or fNIRS.

Results from these 6 studies point to a number of brain regions that are associated with the processing of anti-smoking related messages.

Brain regions mediating emotion regulation

Amygdala

Neuroimaging studies consistently report amygdala activation associated with emotional stimuli (28–30). The amygdala also plays a key role in the acquisition of fear response (i.e. "fear conditioning") by mediating the learning of aversive information. Together with other regions such as the hippocampus and prefrontal cortex, it facilitates the memory of that

information (31, 32). In the domain of GWL research, studies in adults found that amygdala activation was positively correlated with emotional salience of the graphic component of the health warnings (33, 34). Our review indicates that studies in adolescents and young adults generally find similar patterns of activation in the amygdala when viewing health warnings, but also suggests some differences associated with developmental maturation and severity of tobacco use disorder. For example, an fMRI study of young adults comparing the FDA proposed GWLs (consisting of text warnings with emotional images) against control labels with the same text warnings and geometric shapes similar to the graphic image, found greater amygdala activation when viewing the GWLs (26). When comparing brain responses to GWLs between adolescent and adult smokers, Do and Galván (2015) reported that adolescents had less activation in the amygdala when viewing GWLs, but greater impact on reducing craving than in adults. This suggests developmental differences in amygdala sensitivity (35). Importantly, greater amygdala activation in similar adult studies was associated with better post-intervention cessation outcomes (36), suggesting that anti-smoking health warnings targeting the amygdala may improve their efficacy in reducing smoking and preventing smoking initiation. A study by Maynard et al. (2017) examined the effects of severity of tobacco use disorder on brain responses to health messages, by comparing three groups of young adults: non-smokers, weekly smokers, and daily smokers (37). This fMRI and eye tracking study compared GWLs on “branded” vs. plain cigarette packs. They found that when viewing GWLs attached to plain cigarette packs, weekly smokers exhibited decreased activity in the right amygdala, whereas the opposite was found in daily smokers, suggesting that severity of tobacco use disorder plays a role in amygdala response to these health warnings (37).

Hippocampus

Activation of the hippocampus has been reported in a number of studies of adult responses to emotional stimuli (32, 38). In an fMRI study, Wang et al. (2015) found that the hippocampus was co-activated with the amygdala when viewing more emotionally salient GWLs (34). Similar findings were reported in adolescents and young adults; for example, Green et al. (2016) found greater activation of the hippocampus when their young adult cohort viewed GWLs compared to control images (26).

Brain regions mediating executive functions

The development of the prefrontal cortex and other regions responsible for executive control in adolescents lags behind the subcortical regions mediating emotion regulation (39). Nearly all of the studies included in this review observed activation of the prefrontal areas in adolescents and young adults when viewing health warnings.

Medial Prefrontal Cortex

Studies in adults have found that the medial prefrontal cortex (MPFC) response while viewing smoking cessation messages or videos predicts long-term smoking behavior (39, 27, 40). This is consistent with the role of the MPFC in self-related processing, and the positive valuation of external stimuli (41). In addition, activation of the MPFC in response to GWLs and other similar health warnings is a better predictor of population-level effects than self-

reported measures (42). Studies in adolescents and young adults yielded similar observations. Green et al. (2016) observed significant activation of the MPFC in their young adult cohort when viewing GWLs (26). Comparing adolescents' brain responses to anti-drug vs. non-drug PSAs (about various narcotic substances), Ramsay et al. observed differences in MPFC and amygdala activation (43). Furthermore, anti-smoking PSA studies in adults have shown that a similar activation of the MPFC predicted lower urine cotinine at a 1-month follow up visit, linking brain activation associated with PSAs to delayed behavioral changes in smoking consumption (39).

Dorsolateral Prefrontal Cortex

The dorsolateral prefrontal cortex (DLPFC) is known primarily for its role in executive functions such as response inhibition and working memory. It has been shown to be activated in a number of health messages studies. Do & Galván (2015) studied the effects of viewing GWLs on both cigarette craving and neurobiological responses in groups of adolescent and adult smokers and nonsmokers (3). While smokers in both age groups exhibited blunted DLPFC and insula activation relative to nonsmokers, this effect was much greater in adolescent smokers. In addition, the functional connectivity analysis showed that age affects the relationship between amygdala and DLPFC. This indicates weaker regulatory control over the limbic system in adolescents. Ramsay et al. studied a cohort of adolescents in order to identify the brain regions associated with response to anti-drug public service announcements (PSA), which were pre-rated as either strongly or weakly persuasive (43). They found that the strongly persuasive PSAs showed greater activation in the brain regions involved in executive functions, such as the DLPFC, than the weakly persuasive PSAs. They also found that viewing the PSAs engaged regions of the socio-emotional network, including the amygdala and MPFC. In addition, there was greater co-activation between the amygdala and lateral prefrontal cortex while viewing PSAs from the strongly persuasive category. These findings suggest that the more persuasive messages were activating both emotional and executive control functions in adolescents (43).

Electroencephalogram (EEG) Studies

Cartocci et al. (2016) used EEG, galvanic skin response (GSR), and heart rate (HR) monitoring to observe young current smokers, ex-smokers, and non-smokers in a pilot study of anti-smoking PSAs (44). The researchers had participants view "Effective" versus "Ineffective" PSAs and evaluated neurometric indexes including "Approach- Withdrawal", which was measured by the alpha band of cerebral signals, "Effort", measured by the theta band of cerebral signals, and "Emotional", which was aggregated by electrodermal activity and heart rate. The PSAs were defined as either "Effective" or "Ineffective" based on previous official reports that concerned behavior and attitude changes following exposure to the PSA. Researchers found that the perception of the "Effective" PSAs produced significantly higher values in all three indexes, suggesting a better engagement that could potentially lead to positive behavioral changes (quit attempts). Indeed, when using EEG to observe the differences in smokers and non-smokers response to health warnings, Stothart et al. (2016) found that there was strong evidence that smokers have both reduced and delayed "Late Positive Potential" responses to health warnings in comparison to non-smokers (45).

Further, Wang et al. (2015) demonstrated that GWLs that evoked greater emotional response were more effective in dampening smokers' electrophysiological responses towards smoking cues and reducing self-reported craving (25).

Conclusions

Neuroimaging studies in adolescents largely support the hypotheses linking heightened adolescent vulnerability to risky health decisions and behaviors. In particular, vulnerability to nicotine dependence is linked to the morphologically uneven development of various brain regions and systems during this formative period. However, the body of experimental neurophysiological literature on health communication in adolescents remains small. It is imperative that it is extended not only to the domain of visual cue exposure experiments with fMRI and EEG, but also in the domain of "multimodal" studies linking multiple aspects of each individual dataset, for example, studies including genetics, neurocognitive processing of health warnings, and objective behavioral outcomes such as urine cotinine levels.

Neuroimaging research in adolescents faces unique challenges. Unlike in adults, recruitment in adolescents presents certain obstacles. Both assent and parental consent is required. Issues such as participants' fear of inadvertent disclosure of their smoking to their parents may hamper unbiased sampling. Also, school schedule and curriculum create high variability in the availability of school-aged research participants. There are both real and perceived safety concerns regarding the collection of neuroimaging data in adolescents. For example, studies involving ionizing radiation exposure such as PET and SPECT, may have limited added value to the non-invasive methods such as fMRI and EEG. On the other hand, other minimally invasive and portable devices such as functional near-infrared spectroscopy (fNIRS) may be able to contribute additional findings.

Although the prevalence of tobacco cigarette smoking in adolescents has been on a decline in the last decade, the Center for Disease Control reports a concurrent increase in the use of e-cigarettes in this population (46). The tobacco industry is unlikely to miss the opportunity to exploit regulatory uncertainties that surround e-cigarettes. Greater exposure and receptivity to media makes adolescents a prime target for sophisticated industry promotion efforts (47). In established smokers, e-cigarettes may have a harm-reduction and even a therapeutic role (48). However, this is not the case in those not yet addicted to nicotine. Specifically in adolescents, e-cigarette use has been associated with greater rates of subsequent use of tobacco cigarettes (47). Thus, e-cigarettes may act as a gateway to cigarette smoking and all the health concerns that accompany it. The tobacco industry majors have been expanding their share of the e-cigarette market to replace the lost traditional cigarette revenues and it is to be expected that e-cigarette advertising efforts will increase accordingly. Moreover, integrated traditional cigarette and e-cigarette business would allow tobacco companies to coordinate their advertising and marketing of both products.

With this new, less studied form of nicotine delivery gaining popularity, the present review's concerns become more pressing. Health promotion efforts must combat youth exposure to

tobacco advertising, and studies which objectively evaluate the most efficacious ways to do so are more necessary than ever. The findings in this review support the need for continued objective biological and behavioral research on smoking prevention in adolescents and young adults. While there are numerous experimental behavioral studies relevant to adolescent responses to health messaging, neurobiological studies on this topic are scarce. Given the current social climate and proposed national investment in new anti-smoking health campaigns, biological research focused on this most vulnerable population would be needed to identify the most effective ways to communicate with adolescents and young adults about this important public health concern.

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Table 1:
Recent imaging studies on anti-smoking warning messages in adolescents and young adults

AUTHOR	SAMPLE SIZE	AGE	PARTICIPANTS	METHODS	REGIONS OF INTEREST	ASSOCIATION
Ramsay, Yzer, Lucianina, Vohs & MacDonald III	70 (35 male)	M=16.75, SD=1.54	Non-smokers	fMRI	Lateral prefrontal cortex, amygdala, medial prefrontal cortex	More persuasive messages activated both emotional and executive control functions. This pattern of activation was associated with perceived convincingness, which has been shown to lead to behavioral change.
Do & Galván	80 (30 male)	M=17.47, SD=0.70 (adolescent smokers), M=16.05, SD=1.28 (adolescent non-smokers), M=27.19, SD=1.66 (adult smokers), M=27.5, SD=1.7 (adult non-smokers)	Smokers	fMRI	Dorsolateral prefrontal cortex (DLPFC)	Smokers exhibited blunted response in insula and DLPFC in comparison to non-smokers when viewing graphic warning labels (GWLs). Data suggests that GWLs effectively lower cigarette craving, especially in adolescent smokers.
Cartocci, Modica, Rossi, Maglione, Venuti, Rossi, Corsi & Babiloni	7 (gender not reported)	M=22.8	Smokers, Ex-smokers, & Non-smokers	EEG	Left frontal gyrus, frontal areas, right dorsal medial prefrontal cortex	Higher emotional reaction corresponded to the Public Service Announcements (PSAs) higher quality, more persuasive and better remembered, which have in turn been linked to positive behavioral changes.
Maynard, Brooks, Munafó, & Leonards	72 (31 male)	M=24.0, SD=3.0 (non-smokers), M=21.3, SD=2.8 (weekly smokers), M=22.6, SD=4.2 (daily smokers)	Daily Smokers, Weekly smokers, & Non-smokers	fMRI & Eye Tracking	Nucleus accumbens, amygdala	No evidence for pack type-dependent activation in nucleus accumbens between groups. Evidence for a smoking status by pack type interaction within right amygdala. Increase in activity of the right amygdala among daily smokers when controlling for visual attention. Increase in eye fixation on GWLs on plain packs over GWLs on branded packs. Increase in brain region associated with visual attention within primary visual cortex when GWLs were presented on plain packs, suggesting they are more salient than when placed on branded packs.
Green et al.	19 (10 male)	M=22.9, SD= 3.3	Smokers	fMRI	Amygdala, hippocampus, medial prefrontal cortex	Greater amygdala activation when viewing GWLs compared to control images. Greater hippocampal activation when viewing GWLs, suggesting better memory formation of the emotional stimuli. Activation in areas of the medial prefrontal cortex (MPFC) that are involved in self-related processing and positive valuation of external stimuli, which has been linked as a predictor of future cessation behavior.
Stothart, Maynard, Lavis, & Munafó	40 (18 male)	M=22.6, SD= 3.6 (non-smokers), M=22.6, SD=8.3 (daily smokers)	Smokers & Non-smokers	EEG	4 event related potentials: visual P1, visual mismatch negativity, P3, and the late positive potential (LPP)	Greatest differences were observed in higher level cognitive emotional processing. LPP response was delayed and reduced in amplitude amongst smokers. Smokers showed a delayed attentional orientation response and delayed reduced later emotional response. No bias found for an early perceptual bias in smokers' visual perception of health warnings, but overall evidence that smokers are less sensitive to the emotional content of cigarette health warnings.