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Neural correlates of error monitoring in adolescents prospectively predict initiation of tobacco use

Andrey P. Anokhin*, Simon Golosheykin

Department of Psychiatry, Washington University School of Medicine, 660 South Euclid, PO Box 8134, St. Louis, MO 63105, USA

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ABSTRACT

Deficits in self-regulation of behavior can play an important role in the initiation of substance use and progression to regular use and dependence. One of the distinct component processes of self-regulation is error monitoring, i.e. detection of a conflict between the intended and actually executed action. Here we examined whether a neural marker of error monitoring, Error-Related Negativity (ERN), predicts future initiation of tobacco use. ERN was assessed in a prospective longitudinal sample at ages 12, 14, and 16 using a flanker task. ERN amplitude showed a significant increase with age during adolescence. Reduced ERN amplitude at ages 14 and 16, as well as slower rate of its developmental changes significantly predicted initiation of tobacco use by age 18 but not transition to regular tobacco use or initiation of marijuana and alcohol use. The present results suggest that attenuated development of the neural mechanisms of error monitoring during adolescence can increase the risk for initiation of tobacco use. The present results also suggest that the role of distinct neurocognitive component processes involved in behavioral regulation may be limited to specific stages of addiction.

1. Introduction

Adolescence is the period of the highest risk for initiation of substance use, and tobacco remains one of the most frequently used substance in this period. Despite some progress in the reduction of the rates of tobacco use, about 38.1% adolescents initiate cigarette smoking by the 12th grade (Johnston et al., 2014). As the leading cause of preventable disease and mortality in the United States, tobacco use and cigarette smoking in particular represents a major public health problem. Furthermore, emerging evidence suggests that the exposure of the developing brain to nicotine may potentially lead to long-term adverse consequences for brain function and cognition (Naude et al., 2014; van Ewijk et al., 2014). Finally, some evidence suggests that nicotine can facilitate heavier alcohol use due to its ability to counter alcohol's sedative effects when the substances are used together (Funk et al., 2006) and can serve as a "gateway" drug by paving the way to the use of harder drugs (Kandel and Kandel, 2015). A better knowledge of factors increasing risk for tobacco use is essential for the development of more efficient prevention and intervention methods.

The etiology of nicotine addiction involves a complex interplay between genetic predisposition and environmental factors (reviewed in Ray et al., 2009). It is reasonable to expect that individual differences in the liability to nicotine addiction are mediated by relatively distinct neurocognitive processes involved in reward learning and self-regulation of behavior, all of which contribute to the risk for addiction in both additive and interactive way. Identification and characterization of the unique role of each of these "component processes" in addictive behaviors and elucidation of their genetic basis is needed for building an integrative model of addiction. It is important to note that the etiology of addictions is a dynamic process that involves distinct stages such as initiation of drug use, progression to regular use, and the development of dependence on the drug. In particular, genetic factors influencing the risk for initiation of tobacco use appear to be distinct from those affecting progression to regular smoking and nicotine dependence (Heath et al., 2002; Munafo et al., 2004), suggesting distinct underlying biological liability. However, little is known about specific neurocognitive mechanisms operating at different stages of substance involvement.

One of the neurocognitive component processes contributing to addiction risk may be error monitoring, a fundamental mechanism of self-regulation of behavior that involves automatic, largely preconscious detection of the mismatch between the intended and actually executed action and subsequent cognitive and emotional

* Corresponding author. Tel.: +1 314 286 2201; fax: +1 314 286 0091.
E-mail address: andrey@wustl.edu (A.P. Anokhin).

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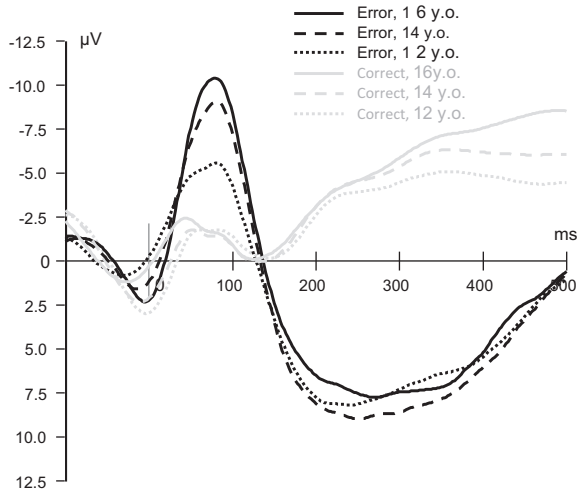

Fig. 1. ERPs elicited by in the flanker task. Response-locked neural activity at the midline frontocentral (FCz) sensor is shown. Motor response is marked by a vertical line. Each waveform represents the signal averaged across trials and participants (grand average) separately for each condition (erroneous and correct responses) and assessment wave (ages 12, 14, and 16).

appraisal of the detected conflict prompting the recruitment of cognitive control for adjustments of ongoing behavior (Segalowitz and Dywan, 2009; van Noordt and Segalowitz, 2012). These stages of error processing are reflected in ERP components associated with commission of errors, the error-related negativity (ERN) and error positivity (P_e) depicted in Fig. 1. Converging evidence from studies using ERP source localization analyses, multimodal imaging (EEG and fMRI), single unit recording, and studies of patients with brain lesions indicates that the main anatomical source of ERN is the anterior cingulate cortex (Debener et al., 2005; Herrmann et al., 2004; Mathalon et al., 2003; Miltner et al., 2003; Ridderinkhof et al., 2004). A previous study in our laboratory has demonstrated significant heritability of individual differences in ERN and P_e components, suggesting that ERN can serve as an endophenotype for disorders characterized by self-regulation deficits (Anokhin et al., 2008). Over the past decade, ERN has been increasingly used in the investigation of neurocognitive mechanisms mediating the risk for psychopathology, including addictive disorders. A thorough review of these studies is beyond the scope of this introduction and we refer the reader to comprehensive reviews on this topic (Moser et al., 2013; Olvet and Hajcak, 2008; van Noordt and Segalowitz, 2012). Briefly, this evidence suggests that increased ERN, presumably indicating abnormally over-active error monitoring system, is associated with obsessive–compulsive, depressive and anxiety-spectrum symptomatology (Aarts et al., 2013b), whereas reduced ERN is associated with personality traits indicating impulsivity, poor socialization, and externalizing symptoms in children and adults (Dikman and Allen, 2000; Hall et al., 2007; Santesso et al., 2005; Stieben et al., 2007). These correlations with psychopathology are broadly consistent with the notion that ERN reflects not only cognitive but also emotional processing of errors (Aarts et al., 2013a; Koban and Pourtois, 2014).

Given this pattern of findings, it is reasonable to hypothesize that deficits in the neural mechanisms of error monitoring may contribute to poor self-regulation of behavior and thus increase the risk for initiation of substance use in adolescents. In particular, a large portion of adolescents (>40%) initiate tobacco use by age 18, despite increasing public awareness of substantial health risks associated with smoking and overall decline in smoking rates. One potential mechanism mediating the hypothesized link between poor action monitoring and tobacco use is impulsivity. This hypothesis is supported by three lines of evidence. First, adolescent smokers tend to score higher on laboratory and self-repot measures of impulsivity (Reynolds et al., 2007), and impulsivity is one of important prospective predictors of smoking initiation in adolescence (O'Loughlin et al., 2014). Second, studies reported associations between reduced ERN and higher impulsivity (Potts et al., 2006), broader externalizing and impulse-control problems (Hall et al., 2007), ADHD (Shiels and Hawk, 2010), and risk-taking (Santesso and Segalowitz, 2009). Third, developmental neuroscience has demonstrated that the brain continues to develop during adolescence. Areas of the prefrontal cortex supporting behavioral regulation are characterized by the longest development lasting into the young adulthood, and their relative immaturity may be responsible for poorer self-regulation of behavior in adolescents compared with adults (Casey et al., 2008; Richards et al., 2012; Spear, 2013). These lines of evidence converge to suggest that the neural mechanisms of action monitoring may be immature and continue to develop during adolescence, and individuals with slower or attenuated development may be more prone to impulsive and risky actions such as experimenting with tobacco and other drugs.

The few studies that investigated ERN in relation to tobacco use yielded mixed results. Luijten et al. (2011) reported reduced ERN in smokers after smoking cues exposure, however, other studies using ERN paradigms without smoking cues found no significant differences between smokers and non-smokers with respect to ERN amplitude (Franken et al., 2010; Rass et al., 2014). In a study using reward and punishment contingencies (Potts et al., 2006), smokers showed ERN reduction but only on punishment-motivated trials. Thus, the question of whether and how error monitoring is related to tobacco use and dependence warrants further investigation. In part, these disparate findings can be attributed to small sample sizes of most studies cited above. Across these studies, results for P_e were also disparate: while two studies (Franken et al., 2010; Luijten et al., 2011) found reduced P_e components in smokers, a recent study (Rass et al., 2014) reported increased P_e in intermittent smokers relative to both non-smokers and regular dependent smokers, with the latter two groups showing no significant differences.

However, the main limitation of previous research has been its correlational nature, i.e. reliance on cross-sectional comparisons between tobacco users and non-users. Due to the well- known fact that correlation does not imply causation, cross-sectional designs preclude strong causal inferences because differences between users and non-users with respect to measures of brain activity can be interpreted both as a marker of predisposition to substance use and as a consequence of substance exposure (Anokhin et al., 1999, 2000). The most powerful approach to delineating determinants and consequences of substance use is a prospective longitudinal design, in which potential biological markers of risk are assessed before the onset of substance use, preferably at multiple time points across development.

The present study addressed the above limitation by using a prospective longitudinal design to examine whether individual differences in the neurophysiological indicator of error monitoring (ERN) assessed during early and middle adolescence can predict tobacco use in emerging adults. Specifically, we hypothesized that adolescents showing smaller ERN components (presumably indicating poorly developed error monitoring mechanisms) will be at greater risk for initiating tobacco use by age 18. We also expected that ERN would increase with age, consistent with previous developmental studies (Tamnes et al., 2013), and hypothesized that individual differences in the rate of development would be associated with risk for tobacco use, such that individuals showing steeper developmental increase in ERN and thus faster maturation of the error-monitoring system will be less likely to use tobacco compared with individuals showing weaker developmental changes.