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Neural Correlates of Response Inhibition in Adolescents Prospectively Predict Regular Tobacco Smoking

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Abstract

Inhibitory deficits have been widely reported and substance abuse, however, it remains unclear whether such deficits represent a determinant or a consequence of substance use. Here we show, using a prospective longitudinal design, that developmental abnormalities in the neural correlates of response inhibition in adolescents increase the risk for subsequent cigarette smoking. Reduced No-Go P3 amplitude, delayed latency of Go P3 peak, and reduced synchrony of neuronal oscillations at age 14 prospectively predicted regular smoking at age 18. The present findings suggest that functional brain correlates of response inhibition represent a developmental marker of risk for future substance abuse.

INTRODUCTION

Tobacco smoking represents a major health problem due to its causal association with a number of serious diseases and has been recognized as the leading cause of preventable death in many countries (Wipfli and Samet, 2015). Initiation and progression to regular smoking typically starts during adolescence (O’Loughlin et al., 2014; Roberts et al., 2015), and smoking may increase the risk for subsequent use of other substances, acting as a “gateway” drug (Chen et al., 2002). Why do adolescents start smoking, despite the awareness about longer-term negative consequences of smoking? Understanding etiological factors in adolescent smoking is very important for designing effective prevention and treatment approaches. Among the multitude of factors associated with increased risk for smoking initiation and transition to regular smoking (O’Loughlin et al., 2014; Roberts et al., 2015), impulsivity is recognized as a major contributing factor (reviewed e.g. in Dinn et al., 2004).

Inhibitory control deficits are particularly prominent in adolescence, presumably due to the delayed maturation of the prefrontal “control” regions relative to sensory cortical areas and subcortical regions, as evidenced by neuromorphological (Yakovlev and Lecours, 1967), neurophysiological (Anokhin et al., 2000; Segalowitz et al., 2010) and, more recently, neuroimaging data (Casey, 2015; Casey et al., 2008; Dayan et al., 2010; Luna et al., 2010; Rubia, 2013). This imbalance between immature prefrontal cortical regions supporting inhibitory control and relatively more mature and active subcortical regions mediating

motivational drives may result in increased propensity to impulsive and disinhibited behaviors such as substance experimentation (Casey, 2015; Crews and Boettiger, 2009).

Several ERP and neuroimaging studies have examined the associations between response inhibition-related neural activity and smoking. Response inhibition tasks typically elicit two major ERP components, the anterior N2 component peaking about 250 ms after the onset of the No-Go stimulus and “anteriorized” P3 component peaking after 350 ms (Bokura et al., 2001; Nieuwenhuis et al., 2004; Nieuwenhuis et al., 2003; Roberts et al., 1994; Salisbury et al., 2004). The frontal No-Go N2 component, interpreted as a correlate of inhibition in earlier studies, more recently has been viewed as manifestation of a conflict between incompatible response tendencies. The conflict account of N2 suggests that N2 reflects detection of a conflict caused by the competition between the execution and the inhibition of a single response (Donkers and van Boxtel, 2004; Gomez et al., 2007; Nieuwenhuis et al., 2003; Smith et al., 2010). The second component, “anteriorized” No-Go P3, has been proposed as a robust marker of the activation of frontal circuitry related to response inhibition (Fallgatter et al., 1997). In contrast to N2, there is stronger evidence linking the No-Go P3 to motor inhibition process (Bekker et al., 2004; Bruin and Wijers, 2002; Donkers and van Boxtel, 2004; Smith et al., 2008). Furthermore, multimodal imaging studies suggest neuroanatomical dissociation of these ERP components, with P3 but not N2 being associated with the preSMA area which plays an important role in motor inhibition (Huster et al., 2013).

An ERP study of adult participants using a Go/No-Go task (Evans et al., 2009) found reduced No-Go P3 amplitude in heavy smokers compared with non-smokers, but no significant differences in task performance. This finding has been corroborated in a more recent study using a Go/No-Go paradigm and involving adolescent participants (age 15 to 18 years) that also reported reduced No-Go P3 amplitude in smokers (Yin et al., 2015). However, another study of young adults using a Go/No-Go task, found amplitude reduction in No-Go N2 but not P3 potential. This discrepancy may be attributed to the fact that the latter study used stimuli with smoking-related content, rather than neutral stimuli as in other studies. Given that impulsivity has been associated with smoking, evidence for reduced No-Go P3 in smokers is in agreement with the finding of association between reduced No-Go (but not N2) and behavioral impulsiveness (Ruchow et al., 2008).

Functional magnetic resonance imaging (fMRI) studies comparing smokers and non-smokers using response inhibition tasks have reported reduced blood oxygenation level-dependent (BOLD) contrast in smokers during response inhibition, with most consistent differences in prefrontal regions involving the anterior cingulate cortex (ACC) and the superior frontal gyrus (de Ruiter et al., 2012; Nestor et al., 2011). A study of adolescent smokers and non-smokers (Galvan et al., 2011) did not find significant group differences, but inhibition-related activity in the medial and lateral prefrontal cortex was negatively correlated with the heaviness of smoking. The authors suggested that smoking can modulate brain function, implying that the observed relationship represents a consequence of smoking, rather than a pre-existing deficit that predates smoking onset.

Taken together, ERP and fMRI studies suggest deficient activation of brain regions critically involved in the inhibition of prepotent but context-inappropriate motor responses in smokers. However, these cross-sectional correlational studies provide limited causal inference, as they are unable to delineate neurodevelopmental determinants and consequences of substance use. We are aware of only one longitudinal study of adolescent smokers (Mahmood et al., 2013) that assessed adolescent smokers and non-smokers aged 16–19 using fMRI, followed them up for 18 months, and found that lower baseline ACC activation in No-Go trials during a response inhibition task predicted more dependence symptoms at the second assessment. However, because this study included participants who had already initiated regular smoking at baseline assessment, it did not clarify the question whether deficits in inhibition-related brain activity represent a determinant or a consequence of smoking.

To address the limitations of the previous literature and provide insight into the direction of causality in the relationship between neural correlates of response inhibition and smoking, we analyzed data from an ongoing prospective longitudinal study in which a large cohort of adolescents was administered a Go/No-Go task with ERP recording at age 14 and was followed up through age 18. Based on previous ERP studies suggesting a reduction of anterior No-Go P3 potential in adult (Evans et al., 2009) and, importantly, adolescent (Yin et al., 2015) smokers, as well as evidence for strong heritability of No-Go P3 (Anokhin et al., 2004), we hypothesized that a deficit of inhibition-related frontal brain activity during adolescence represents a developmental risk factor for smoking. Accordingly, we expected that reduced No-Go P3 amplitude, a neurophysiological indicator of response inhibition, assessed in early adolescence would prospectively predict cigarette smoking in late adolescence.

Furthermore, we expected that future smokers would also exhibit altered inhibition-related neural oscillations. Recent research suggests that averaged ERPs provide only a limited insight into the underlying event-related neural dynamics, whereas single-trial analysis techniques permit the separation of phase and amplitude effects giving rise to the averaged ERP waveform (Fell et al., 2004; Makeig et al., 2004; Makeig et al., 2002; Onton et al., 2006; Roach and Mathalon, 2008). It has been long known that averaged sensory evoked potentials emerge largely as a result of phase resetting and synchronization of the ongoing EEG oscillations as well as modulation of their amplitude (Livanov, 1934; Livanov, 1977). Synchronization of rhythmic oscillation has traditionally been viewed as a fundamental mechanism of spatiotemporal organization of neural activity within and among distributed neuronal assemblies into coherent functional networks supporting cognition and behavior (Livanov, 1977). Evidence from human and animal studies indicates that transient phase synchronization of oscillations provides precise temporal coordination of neuronal activity states necessary for successful inter-neuronal communication (Buzsaki and Draguhn, 2004; Klimesch et al., 2007; Livanov, 1977; Llinas et al., 2005; Sauseng and Klimesch, 2008; Uhlhaas and Singer, 2010, 2012). Importantly, deficient event-related synchronization of brain oscillations has been associated with cognitive deficits and neuropsychiatric disorders (Uhlhaas and Singer, 2010). In a recent study, we have shown that No-Go ERPs elicited in a response inhibition task emerged largely due to event-related synchronization of cortical neuronal oscillations, such that No-Go stimuli produced stronger phase synchronization in the anterior scalp regions in a time window between 300 and 600 ms after stimulus-onset

compared with Go stimuli (Muller and Anokhin, 2012). Other studies provided convergent results indicating inhibition-related increases in phase synchronization at anterior sites (Beste et al., 2011; Papenberg et al., 2013). Based on this evidence and a general hypothesis postulating that reduced inhibitory control represents a risk factor for addiction we expected that future cigarette smokers would show diminished power and synchrony of event-related oscillations in No-Go trials. Finally, we expected that smokers would make more commission errors on No-Go trials and respond slower on Go trials relative to non-smokers.

METHODS

Participants

Participants were adolescent twins taking part in a longitudinal study of Genetics, Neurocognition, and Adolescent Substance Abuse (GNASA). All participants were recruited from the local population using the state birth records database, therefore, the sample is largely representative of the general population. Exclusion criteria were minimal and included a history of serious head trauma and health conditions precluding a laboratory visit or the ability to perform the experimental tasks (e.g. severe visual impairment or mental retardation). For the present analyses, we used data from the CPT task (described below) administered to participants at age 14 and an in-person semi-structured interview containing questions about tobacco smoking administered at age 18. The final sample with available ERP data at age 14 and interview data at age 18 was $n=431$ (see Statistical Analyses below for details). The study was approved by Washington University Institutional Review Board, and written informed assent and consent was obtained from adolescent participants and their parents, respectively, after complete description of the study to the subjects and their parents.

Procedure

Participants were administered a cued Go/No-Go Continuous Performance Task that has been shown to be a reliable measure of response inhibition in previous studies (Fallgatter et al., 1997; Fallgatter et al., 1999; Fallgatter and Strik, 1999). A series of 400 letters was presented sequentially, one at a time, for 0.2 s with a constant stimulus onset asynchrony of 2s (Fig. 1). Participants were instructed to respond as quickly as possible to the letter X (a Go stimulus) by pressing a button on the response pad with their right index finger. Importantly, X was always preceded by O which effectively served as a warning stimulus triggering response preparation (O-X sequence). However, participants had to withhold their response when the letter O was followed by any other letter than X (O-not-X combination such as O-Z, O-K, etc.). Response speed and accuracy were equally emphasized. A total of 400 letters were presented, of which 80 (20%) were cue stimuli (the letter “O”), 40 (10%) were Go stimuli (X following O), 40 (10%) were No-Go stimuli (any letter other than X following O), and the remaining 240 stimuli were neutral “fillers” (12 different letters not including O or X). Thus, the O-X combination represented a Go trial, whereas any O-not-X combinations represented a No-Go trial, and there were a total of 40 O-X (Go) and 40 O-not-X (No-Go) trials in the task presented in a pseudo-random order. The letter O served as a warning cue informing the subject that the next stimulus is likely to be a Go signal and thus triggered a motor preparation and response prepotency. A No-Go stimulus (any letter other than X) presented after O required withholding of the pre-activated response. It is

important to note that equal probability of Go and No-Go stimuli ensured that Go versus No-Go differences are not confounded with oddball effects that are typically observed when stimuli differ in their frequency.

Cigarette smoking was assessed using a face-to-face interview at age 18. Participants were categorized as “regular smokers” if they reported having smoked 100 cigarettes in one’s life, a definition of a “smoker” according to the Centers for Disease Control and Prevention (CDC, 2002; Jamal et al., 2015) that has been employed in large national epidemiological studies. This measure was particularly appropriate for the current sample of late adolescents because it allowed us to identify individuals who have already progressed to regular smoking, but may not have yet developed dependence, which typically occurs when regular smoking is already established. Since most smoking onsets took place between ages 16 and 18, individuals who started smoking relatively recently may not have smoked regularly long enough to develop dependence by the age of assessment (18). In addition, we also used a measure of smoking initiation (ever smoking) defined as having smoked at least one cigarette during lifetime.

ERP recording and pre-processing

The EEG was recorded from 30 scalp locations according to the extended 10–20 system using an elastic cap with Ag/AgCl electrodes and a ground electrode on the forehead, with high- and low-pass filters set at 0.05 and 100 Hz, respectively. The left mastoid served as reference, and an averaged mastoid reference was digitally computed off-line using the right mastoid recording as a separate channel. Vertical electro-oculogram recording was used for eyeblink artifact correction using a regression-based procedure (Semlitsch et al., 1986). After screening for artifacts, EEG signals were subjected to 30 Hz low-pass filtering, and 1-s epochs time-locked to the stimulus were extracted (from –0.1 to 0.9 s relative to the stimulus onset), baseline-corrected, and averaged separately for correct Go and No-Go trials (correct button press and withholding of the response, respectively). The P3 peak was detected as the most positive voltage value within 250–500ms window, and scored as absolute amplitude relative to the averaged baseline.

Averaged ERPs provide only a limited insight into event-related neural dynamics (Cohen, 2011; Fell, 2007; Mathalon and Sohal, 2015). It has been shown that ERPs result from a superposition of neuronal oscillations at different frequencies that are phase-locked to the stimulus onset (Fell et al., 2004; Livanov, 1979; Makeig et al., 2002). In particular, a previous study has shown that response inhibition and production in the Go/No-Go task is supported by a distinctive pattern of synchronized neuronal oscillations (Muller and Anokhin, 2012). Therefore, to gain a more detailed insight into the neurophysiological processes associated with response inhibition, we used methods for single-trial time-frequency analysis of event-related cortical oscillations.

Time-frequency decomposition was performed using EEGLAB toolbox (Delorme and Makeig, 2004) running under MATLAB software. The frequency range analyzed was 1 to 30 Hz, and the analysis epoch was 3000 ms (–1000 to 2000 ms relative to the stimulus onset). We computed event-related spectral perturbation (ERSP), a measure of mean event-related changes in the power spectrum of ongoing neuronal oscillations, using a Morlet wavelet to

assess log power at each time and frequency bin. To obtain better frequency resolution at higher frequencies, we used wavelets with the number of cycles is increasing with frequency (Delorme and Makeig, 2004). The log power spectrum was baseline-normalized by subtracting the mean baseline log power spectrum from each spectral estimate, thus post stimulus activity represented spectral differences from the pre-stimulus baseline (−500 to 0 ms) expressed in decibels (dB). In the resulting time-frequency plots (Figures 3 and 4, panel A), the color of each image pixel represents change in spectral power relative to pre-stimulus baseline (in dB) at a given frequency and latency.

Next, we assessed inter-trial phase coherence (ITC), also called phase-locking index (PLI), a measure of synchronization of brain oscillations at a particular frequency and latency. Using a cosine function centered at stimulus onset as an event-phase indicator function, spectral estimates of oscillatory activity in individual trials were represented as a complex vectors in the 2-D Cartesian space (magnitude and phase). ITC was computed by first normalizing the length of trial activity vectors to 1 and computing a complex average over trials, which resulted in an ITC measure that is sensitive to phase but not magnitude of the spectral estimate (Delorme and Makeig, 2004).

Both ERSP and ITC analyses were conducted separately for Go and NoGo trials, and the two conditions were compared using a paired t-test in order to identify areas in the time-frequency space that show the largest and most significant difference between No-Go and Go conditions while controlling for false-discovery rate using Benjamini-Hochberg approach (Benjamini and Hochberg, 1995). Finally, for statistical analyses with smoking variables we extracted average values of ERSP and ITC within rectangular regions of interest (ROIs) in the time-frequency space defined by the time frame and frequency range (theta-band response: of 250–450 ms, 3–8 Hz; alpha-band response: 250–400 ms, 8–13 Hz). The selection of ROIs was driven by the following considerations: greater activation in No-Go compared with Go trials (Fig. 3A), temporal overlap with the N2/P3 complex, and correspondence to conventional EEG frequency bands (theta and alpha).

Statistical analysis

The indices of brain activity at age 14 described above (amplitude and latency of P3, ERSP, and ITC in Go and No-Go condition) were used as independent variables (predictors) in logistic regression analyses with regular smoking status at age 18 (yes, no) as a categorical dependent variable.

Since preliminary analyses showed a significant effect of gender on the No-Go P3 (P3n) component indicating somewhat larger amplitudes in males ($F(1,612)=9.26$, $p<.01$ at FCz and $F(1,612)=4.17$, $p<.05$ at Cz), and gender was significantly associated with regular smoking status at age 18 (Chi-squared 9.67, $df=1$, $p<.01$), with higher prevalence in males, gender was included as a covariate in all analyses to control for potential confounding. To avoid further confounding by ethnicity, the analysis was restricted to Caucasian individuals only who constituted the majority of the sample. Our preliminary analyses showed significant ethnic differences in both ERPs and smoking rate, however, the number of regular smokers among black participants in the current sample ($n=2$) was too small to include ethnicity as a covariate.

Exploratory analyses of smoking variables have shown that among individuals with ERP data ($n=452$), 149 participants (33%) have tried cigarettes and 51 (11.3%) became regular smokers by age 18. Of the total sample, 21 participants (4.6%) have tried cigarettes already at age 14; these individuals were at more than 4-fold higher risk for becoming regular smokers by age 18 ($\chi^2=21.93$, $df=1$, $p<.001$). These early-onset smokers were excluded from statistical analyses in order to rule out any causal effects of smoking on brain function at age 14. In the remaining sample ($n=431$), 42 individuals were regular smokers, while 389 individuals did not meet the >100 cigarettes criterion.

Next, we conducted follow-up analyses to establish the specificity of findings to regular smoking rather than smoking initiation. First, we examined whether brain activity measures predicted smoking initiation (having smoked at least one cigarette during lifetime). Second, we examined associations with a “smoking progression” variable, i.e. transition to regular smoking ($n=42$) among those who tried cigarettes ($n=149$).

RESULTS

Averaged ERP waveforms elicited in Go and No-Go trials are shown for all 30 scalp locations in Fig. 2. Successful response inhibition was associated with a prominent fronto-central P3 component, in contrast to correct Go trials which elicited a P3 component peaking at the mid-parietal (Pz) location. This “anteriorization” of P3 in the No-Go condition is highly consistent with previous ERP studies of response inhibition (Fallgatter and Strik, 1999; Roberts et al., 1994). To test for significance of these apparent topographical effects, we conducted repeated measures ANOVAs with P3 amplitude as a dependent variable using within-subject factors Electrode (5 levels: midline electrode chain including Fz, FCz, Cz, Cpz, and Pz) and Condition (2 levels: Go, No-Go) with Greenhouse-Geisser correction of the degrees of freedom for deviations from the sphericity assumption. A critical test for topographical differences between conditions is Electrode $\times$ Condition interaction, which was highly significant $F(4,1121.2)=967.6$, $p<.001$.

Time-frequency decomposition of event-related EEG oscillations (Fig. 3) showed an increase in power and synchrony in the No-Go relative to Go condition in the midline frontocentral area (FCz).

Consistent with our prediction, regular smoking at age 18 was significantly predicted by decreased No-Go P3 amplitude, but there was no association with Go P3 amplitude (Fig. 5 A and B, Table 1). Analysis of peak latencies of these components revealed delayed Go P3 responses in future smokers, however, contrary to our prediction, there was no significant effect of No-Go latency. Analysis of event-related spectral perturbations (ERSP) showed that reduced power of theta- and alpha- oscillations elicited by No-Go stimuli significantly predicted future regular smoking (Fig. 2, 6). This finding was paralleled by diminished inter-trial phase coherence in future smokers indicating a weaker event-related neural synchrony in theta and alpha frequency bands (Fig. 2, 6).

Analysis of performance data (false alarm rate in No-Go trials and median reaction time in correct Go trials) did not show significant differences between smokers and non-smokers, although there was a non-significant trend ($p=.087$) toward slower reaction time in smokers.

To provide additional validation for the measure of regular smoking (100+ cigarettes smoked during lifetime), we analyzed the relationships between this measure and other metrics of tobacco use available in the semi-structured interview. Regular smoking showed highly significant associations with age at smoking onset ($F(1,238)=45.9$, $p<0.001$, earlier onset in regular smokers), number of days smoked in the past 12 months ($F(1,153)=98.6$, $p<0.001$), weekly smoking ($\chi^2 = 427.7$, $df=1$, $p<0.001$) and daily smoking ($\chi^2 = 427.7$, $df=1$, $p<0.001$). Thus, individuals meeting the “100+ cigarettes” criterion for regular smoking and those who do not meet this criterion show large and highly significant differences with respect to other measures of quantity and frequency of cigarette use, indicating that the current definition of regular smoking is a potent indicator of maintenance and escalation of tobacco use following the initial experimentation phase.

In contrast to regular smoking, smoking initiation (having smoked a single cigarette or even a puff) showed no significant associations with ERP amplitudes or latencies in logistic regression analysis, however, both ERSP and ITC measures of alpha-band event-related oscillatory dynamics in the No-Go trials significantly predicted smoking initiation by the age of 18 ($p=.006$ and $p=.008$, respectively).

Finally, we examined whether neurophysiological measures of response inhibition are specifically related to transition from cigarette experimentation to regular smoking by restricting the analysis to those participants who had initiated smoking by age 18 and using the “smoking progression” phenotype (whether or not one progresses to regular smoking, given initiation) as a dependent variable in the logistic regression analysis. All ERP and time-frequency variables showing significant effect on regular smoking in Table 1 also significantly predicted smoking progression.

DISCUSSION

The main conclusion from the present findings is that deficient frontal neuronal activity related to response inhibition is associated with increased risk for becoming a cigarette smoker. To our knowledge, this study is the first to address the direction of causality in the relationships between inhibition-related brain activity and smoking using a prospective longitudinal design. The present results provide a novel evidence that alterations in brain activity previously reported in smokers predate the onset of smoking and represent a pre-existing factor of risk, rather than a consequence of smoking. Importantly, the present results show relative condition specificity with respect to response inhibition, since most of the group differences occur in No-Go condition, with a notable exception of increased latency of Go P3 in smokers. The results also show topographical specificity, since group differences are concentrated in the midline frontocentral region of the scalp (see below for a more detailed discussion).

The present study employed two different approaches to quantify neurophysiological activity related to response inhibition: the traditional averaged ERPs and time-frequency analysis of event-related brain oscillations. Data from both analyses provide convergent evidence that neuronal activity in the time window from 250 to 400 after the onset of the No-Go stimulus differentiates between future smokers and non-smokers. The convergence of ERSP and ITC data suggests that increase in power in this time window is associated with stimulus-induced phase reset of brain oscillations that ensures a precise timing of the neuronal activity required for rapid resolution of the conflict between prepared motor response and the need to inhibit it (Huster et al., 2013; Muller and Anokhin, 2012). A reduction of both phase consistency and power of brain oscillation may indicate disrupted neural synchrony in adolescents at high risk for becoming regular smokers. This interpretation is consistent with the evidence for reduced power of inhibition-related brain oscillations in offsprings of alcoholics (Kamarajan et al., 2006; Pandey et al., 2015). Taken together, the present findings and previous literature suggest that weakened neuronal synchrony in situations of increased inhibitory demand may constitute a biomarker of inherited risk for a broad spectrum of addictive behaviors characterized by failures of inhibitory self-control.

Interestingly, the time frequency plots in Fig. 4 indicate group differences in two consecutive time windows: the earlier effect occurs at about 180 ms after the stimulus onset, followed by a second difference at around 300 ms. This biphasic time course may reflect two distinct consecutive processes: conflict detection (the need to inhibit a prepared response) and actual implementation of inhibition. Further, more refined analyses of synchronized oscillatory activity in response inhibition tasks are needed to determine how these processes are related, e.g. whether imprecise stimulus categorization at the earlier stage negatively affects the downstream processes, or these two temporal “phases” of group differences represent independent deficits.

It is important to note that, while EEG provides an insight into fine timing of neural and cognitive processes underlying the processing of Go and No-Go stimuli, its spatial resolution is very limited. Nevertheless, topographical data presented in Figures 2–4 show that all effects of interest converge on the midline frontocentral region of the scalp situated above the dorsal ACC, medial prefrontal cortex, and superior prefrontal gyri, including the supplementary motor area – regions critically involved in inhibition of motor responses. This topographical distribution is consistent with available evidence for neuroanatomical localization of No-Go ERP components in the ACC and adjacent areas of the medial frontal cortex (Bekker et al., 2005; Fallgatter et al., 2002; Garavan et al., 2002; Jonkman et al., 2007; Mathalon et al., 2003; Swainson et al., 2003; van Veen and Carter, 2002a, b). A recent multimodal imaging study using simultaneous acquisition of EEG and fMRI showed associations of No-Go P3 amplitude with activation in a broader network of regions including the left anterior insula, inferior frontal gyrus, and posterior cingulate (Baumeister et al., 2014).

Another important finding is that deficits in neurophysiological substrates of response inhibition were primarily associated with regular smoking rather than initiation of smoking. Furthermore, the convergence of results obtained using the “regular smoking” phenotype and more restricted “smoking progression” phenotype suggests that the observed

relationship between regular smoking and No-Go ERPs and oscillatory dynamics arises primarily due to the effect of inhibitory processing deficits on the transition from initial experimentation with cigarettes to regular smoking. The only exception was reduced event-related oscillatory dynamics (power and synchrony) in the alpha band, which was significantly associated with both initiation and progression measures. In this connection, it is interesting that a recent study found an association of diminished error-related negativity (ERN), a neural correlate of error monitoring, with smoking initiation but not transition to regular smoking (Anokhin and Golosheykin, 2015). Together, these findings suggest that different cognitive control processes, both localized in the ACC and adjacent medial prefrontal cortex, are associated with distinct stages of addiction. This double dissociation underscores the complexity of the neurocognitive underpinnings of addictive behaviors. However, this dissociation is unsurprising, given evidence from genetic studies that smoking initiation and progression to further stages of tobacco involvement such as persistent smoking and nicotine dependence are influenced by distinct, although partially overlapping genetic factors (Heath et al., 2002; Munafò et al., 2004). It is likely that the liability to nicotine addiction is mediated by relatively distinct etiological factors including different neurocognitive processes involved in reward learning and self-regulation of behavior which may contribute to the risk for addiction in both additive and interactive way. Building an integrative etiological model of addiction will require characterization of the unique role of each of these “component processes” in addictive behaviors and elucidation of their dynamic interplay during individual development.

The lack of significant relationship between smoking and performance measures (accuracy and latency) is in line with some of the previous studies that yielded mixed results regarding the relationship between smoking and behavioral measures of response inhibition (Chamberlain et al., 2012; Evans et al., 2009; Galvan et al., 2011; Monterosso et al., 2005; Yin et al., 2015). The lack of significant correlations with performance in the present study may have at least two explanations. First, the task was fairly easy, resulting in a “floor effect” on false alarms, and the restricted range of variability severely limited the analysis of performance accuracy data. Second, it is possible that the subtle alterations of inhibition-related neural processing may not be sufficient to affect performance in a simple and straightforward task, perhaps due to compensatory mechanisms, but may still affect more complex behaviors in the long run, leading to increased vulnerability to regular smoking.

A delayed P3 peak latency in Go trials and a trend ($p=.087$) toward longer reaction time in future smokers are consistent with compensatory motor slowing to deal with the challenge posed by the presence of No-Go trials. Compared with the classical oddball task, in which all rare targets are Go stimuli, the equal probability of Go and No-Go trials in the current task creates a Go-NoGo conflict which may affect responses not only to No-Go, but also to Go stimuli. The nature of the stimulus following the warning cue (letter O) is totally unpredictable, and this uncertainty imposes higher cognitive control demands even in the Go trials compared with a standard oddball task. It can be speculated that future smokers may have limited cognitive control capacity and need more time for resolution of the Go-NoGo conflict (i.e. selection of appropriate action) in order to maintain accurate performance, which results in a delayed motor command.

Finally, by restricting analysis to only those individuals who were completely tobacco-free at the time of neurophysiological assessments (age 14), we ruled out possible causal effects of early smoking on brain function. Controlling for these effects allows us to make a stronger causal inference and conclude that alterations in the neurophysiological correlates of response inhibition represent a developmental deficits predating smoking onset, rather than a causal effect of smoking.

Several limitations of the present study need to be acknowledged. First, the present findings strongly suggest that deficits in inhibition-related neural activity predate the smoking onset and are thus related to pre-existing risk, rather than consequences of smoking. However, this does not exclude the possibility that regular smoking, once established, can produce further impairments in the neural mechanisms of response inhibition. Future analyses of data from this ongoing study will test the hypothesis whether the length of and heaviness of regular smoking is associated with additional impairments in brain function after controlling for group differences that preceded smoking onset. Second, because of the low prevalence of nicotine dependence in this adolescent sample, we did not have sufficient power to contrast dependent versus non-dependent smokers. It is important to note that due to relatively recent smoking onset before the current assessment, nicotine dependence measure would be highly censored in the statistical sense because key symptoms such as impairment of functioning may not have developed yet in these young smokers. It is important to note that from the public health perspective, regular smoking may be more important than dependence because regular smokers expose themselves to harmful effects of smoking regardless of their dependence. We acknowledge, however, that the definition of regular smoking is based on arbitrary cut-off, however, this definition has been endorsed by the Center of Disease Control (CDC), used in epidemiological and genetic studies of smoking, and is considered as a major milestone in transition to regular tobacco use. It is important to note, that this measure correlates strongly with other metrics of tobacco involvement such as quantity and frequency of smoking. Finally, electrophysiology methods provide a limited insight into the underlying neuroanatomy. Although the link between response inhibition-related ERPs, ACC, and other prefrontal cortical areas is fairly well established, the activity of relevant subcortical brain regions such as basal ganglia is difficult to detect using scalp-recorded EEG. Multimodal imaging studies combining EEG and fMRI methods are strongly warranted because, by capitalizing on the superior spatial resolution of fMRI and superior temporal resolution of the EEG they can provide the most complete picture of neural processes and mechanisms mediating the risk for nicotine addiction.

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Figure 1.

The cued Go/No-Go Continuous Performance Task (CPT). The letter O serves as a warning cue alerting the subject about the impending Go stimulus and thus creates a response prepotency. An X following O represents a Go stimulus that requires a speeded response; any other letter following O is a No-Go stimulus. Go and No-Go stimuli (O-X and O-non-X combinations, respectively) occur in a pseudo-random order with an equal probability (40 combinations of each type out of 400 letters in total; all other letters represent neutral distracters). Thus, the relatively rare Go stimulus (10% of all letters) in this task is similar to an oddball stimulus in a classical oddball task. Equal probability of Go and No-Go stimuli allows to avoid the confounding of the No-Go effect with an oddball effect.

Figure 2.

ERPs during the Go/No-Go task (top view of the head, nose up). Voltage negativity is plotted up, positivity is down. The vertical line indicates the stimulus onset. ERPs in Go trials (green line) are superimposed on the ERPs in the No-Go trials (red line) to facilitate comparison between conditions. Note the “anteriorization” of the P3 potential: In the Go condition, which is similar to the classic “oddball” condition, the P3 component peaks at the mid-parietal (Pz) area, whereas in the No-Go condition P3 is attenuated in parietal areas and increased in central and frontal areas, peaking at Cz.

Figure 3.

Event-related neuronal oscillations in the Go/No-Go task: increased power and synchrony in the No-Go relative to Go condition in the midline frontocentral area (FCz). A. Event-Related Spectral Perturbations (ERSP): time course of changes in the spectral power of neuronal oscillations at different frequencies elicited by Go and No-Go stimuli relative to the pre-stimulus baseline. Horizontal axis: time in milliseconds (ms); 0 indicates the stimulus onset. Vertical axis: frequency, Hz. Color scale shows the change relative to the baseline in decibels (dB). Topographical maps (top view of the head, nose up) show the distribution of the mean values extracted from the region of interest (250–400 ms, 8–13 Hz). B. Inter-Trial Coherence (ITC) shows changes in neural synchrony (phase consistency of oscillations across trials).

Figure 4.

Regular smokers show attenuated power and reduced synchrony of event-related neuronal oscillations in No-Go trials in the midline fronto-central area. A. Event-Related Spectral Perturbations (ERSP) assessed at age 14 in individuals with (RS+) and without (RS-) a history of regular smoking at age 18. The lower panel shows areas of significant RS– - RS+ differences in theta, alpha, and beta1 frequency bands. Topographical maps (top view of the head, nose up) show the distribution of the mean values extracted from the region of interest (250–400 ms, 8–13 Hz). B. Inter-Trial Coherence (ITC) shows group differences in neural synchrony (phase consistency of oscillations across trials).

Figure 5.

Event-related potentials (ERPs) in the Go/No-Go task assessed at age 14. A. Go trials, mid-parietal area (Pz). B. No-Go trials, mid-central area (Cz). RSm+ and RSm- represent grand-averaged waveforms for participants with and without history of regular smoking by age 18, respectively. A vertical dashed line at zero time indicate the onset of the stimuli. Note that peak and latency of grand-averaged waveform provides only an approximate representation of the averages of individual peaks and latencies (see Figure 6).

Figure 6. Group differences in event-related brain activity at age 14. Future regular smokers show (A) reduced amplitude of the No-Go P3 component, (B) delayed latency of the Go P3 peak, (C) attenuated power of theta-band oscillations in No-Go trials, and (D) reduced theta-band neural synchrony in the No-Go trials. Error bars represent standard error of the mean; * $p < 0.05$. ** $p < 0.01$.

Table 1

Prospective associations between brain activity measures at age 14 and regular smoking status by age 18.

Brain activity measure	B	±S.E.(B)	Wald	p-value	Exp(B)
NoGo P3, amplitude	-.034	.017	4.10*	.022	.967
NoGo P3, latency	.000	.003	.003	.477	1.000
NoGo_ERSP, Theta	-.266	.096	7.69**	.003	.766
NoGo_ERSP, Alpha	-.280	.099	8.03**	.003	.756
NoGo_ITC, Theta	-3.156	1.17	7.24**	.004	.043
NoGo_ITC, Alpha	-4.31	1.51	8.16**	.002	.013
Go P3, amplitude	-.004	.018	.041	.420	.996
Go P3, latency	.008	.003	8.44**	.002	1.008
Go_ERSP, Theta	-.054	.097	.31	.290	.948
Go_ERSP, Alpha	-.103	.095	1.18	.139	.902
Go_ITC, Theta	.82	1.32	.38	.269	2.260
Go_ITC, Alpha	1.604	1.76	.83	.181	4.971

ERSP (Event-Related Spectral Perturbations) and ITC (Inter-Trial Coherence) measures represent regions of interest in the time-frequency space defined by the time frame and frequency range (Theta-band response: of 250–450 ms, 3–8 Hz; Alpha-band response: 250–400 ms, 8–13 Hz). B is the coefficient estimate for the logistic regression equation for predicting regular smoking status at age 18 from the neurophysiological variable measured at age 14. S.E. is the standard error of B. Wald's chi-square value is presented for testing the null hypothesis that the regression coefficient (B) is zero, along with the corresponding p-values (one-tailed). Exp(B) is the exponentiation of the regression coefficient B representing odds ratios for the neurophysiological predictors.