



Research report

Neural correlates of response inhibition in current and former smokers

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HIGHLIGHTS

- Response inhibition in current, former and never smokers was behaviorally similar, but differed in the neural recruitment of the cerebellum.
- Despite similar task performance across groups, errors differentially activated regions involved in attention and motor control.
- Regions other than the IFG and dACC should be considered when investigating response inhibition in addiction, especially in older populations.
- Discussion emphasizes the role of compensatory processes and promotes a connectivity approach to neural processes in addiction.

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ABSTRACT

Loss of behavioral control is a hallmark of addiction. Individual differences in basic cognitive processes such as response inhibition may be important for interrupting automatic behaviors associated with smoking and supporting prolonged abstinence. To examine how response inhibition and error monitoring processes differ as a function of smoking status, current smokers, former smokers and never smokers (N = 126) completed a simple Go/No-Go task while undergoing functional magnetic resonance imaging. All groups performed similarly on the task and similarly engaged the inferior frontal gyrus and dorsal anterior cingulate cortex, regions traditionally associated with response inhibition and error monitoring, respectively. During response inhibition (i.e., Correct Rejects > Hits contrast), overall group differences emerged in the recruitment of the cerebellum, while individual group differences in error monitoring (False Alarms > Hits contrast) were seen for regions of the parietal lobe and thalamus (current smokers > former smokers), as well as regions of the bilateral cerebellum, parahippocampal gyrus and superior parietal lobe (i.e., ever smokers > never smokers). We discuss how our results replicate two previous large-sample studies that used the same Go/No-Go task and review these data in terms of network models of inhibitory and error monitoring abnormalities in addiction.

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1. Introduction

Addiction is a complex condition often associated with efforts to control substance use that is followed by subsequent relapse and loss of control over substance use. Addiction reflects behavior driven by reinforced schemas of actions that are cued, consciously or non-consciously, by the environment and/or through changes in homeostatic states of positive and negative affect [1]. Importantly,

once initiated these automatic behaviors are very difficult to interrupt or suppress, which can lead to the loss of behavioral control over drug use. When, and if, behavior change is attempted then it becomes a battle between “bottom-up”, or cue-driven, processes that support drug-seeking behaviors and “top-down”, or goal-directed, behaviors that are supported by processes of cognitive control. In this way, processes that support top-down control become an important weapon in the battle for behavioral change.

The view that behavior change depends on top-down control is echoed in several models of addiction [2–6]. Although the models differ in their details, a shared element is that effortful, top-down, control is necessary to stop unwanted behaviors, and circuits of the prefrontal cortex (PFC) support this control [7–10]. One process of

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top-down control explicitly linked to behavioral change is response inhibition [4,5]. Response inhibition is defined as the ability to withhold a prepotent response in a context-appropriate manner [11,12], and reflects a set of component processes that are needed to interrupt habitual responding in favor of an alternative behavior (e.g., smoking cessation). The Go/No-Go task [13] is a common measure of response inhibition that often shows performance decrements in individuals with substance use disorders (for a review of the existing neuroscience literature see Ref. [14]). The basic principle of the Go/No-Go task is straightforward: individuals are presented with rules that indicate how they should respond to a particular stimulus (i.e., Go trials), and the conditions that require an alternative, or inhibited, response (i.e., No-Go trials). The Go/No-Go task is a popular measure of response inhibition [15–23] in part, because variants on the task allow for parsing of specific cognitive processes (e.g., response inhibition, orienting, error awareness, etc. [24,25]). For example, one can modify the task to place heavy demands on processes of response inhibition by increasing the ratio of Go trials to No-Go trials, or one can make the task more challenging and error-prone by modifying the rules that govern when to inhibit a response. It is important to note that the flexibility of the Go/No-Go task makes it a useful measure for both the clinic and laboratory, but it can lead to differences in interpretations, especially with respect to neuroanatomical contributions to response inhibition and error monitoring [26,27], a theme that we will revisit in the discussion.

Performance deficits on Go/No-Go tasks have been observed in cocaine users [28] (see Refs. [29,30] for similar findings using a stop-signal task), cannabis users (for error-awareness, [31]), and alcohol users (using an alcohol Go-No-Go task, [32]; see Ref. [33] for similar findings using a stop-signal task), an effect compounded by acute exposure to alcohol and/or low baseline working memory [34,35]. The observation that individuals with substance use disorders demonstrate impaired performance on measures of top-down control (e.g., the Go/No-Go task and stop-signal task), has led to the hypothesis that behavior change is difficult, in part, because short-term abstinence negatively influences those top-down systems of restraint, or control, that one would otherwise use to support goal-directed behavior. The domain of nicotine dependence seems to support this hypothesis. Studies have shown that short-term nicotine abstinence impairs performance on measures of top-down control [36–38], while the administration of nicotine improves top-down control [39], but see Ref. [40]. Both short-term (e.g., 1 week) and longer-term (e.g., 1 month) cessation are related to processes that support top-down control [41–43], and pharmaceutical interventions to support smoking cessation also improve processes related to top-down control [44]. Finally, administration of nicotine improves the affective symptoms of cognitive withdrawal in smokers (for a review see Ref. [45]), and reduces the experience of psychological stress [46], which might indirectly influence top-down processes [47].

Behavioral deficits in response inhibition as measured by the Go/No-Go task have produced mixed results with respect to nicotine dependence. Spinella [48] found that the number of inhibition errors committed on a tapping Go/No-Go task correlated negatively with the number of cigarettes smoked per day. However, Dinn and colleagues [49] found no difference in the performance (accuracy or reaction time) between smokers and nonsmokers on three different versions of a Go/No-Go task. This suggests that further work is needed to understand how processes of response inhibition might differ in smokers and how these differences might manifest in the brain. Importantly, it is currently unknown if any deficits observed in smokers on the Go/No-Go might persist following long-term smoking cessation. In a study of attention bias, former smokers (with an average of 6.5 years abstinence) appeared to overcome their bias towards smoking related images, suggesting there are

some changes to the cognitive system following long-term abstinence [50]. Similarly, Mons et al. [51] found that neurocognitive deficits were less prominent in a sample of older former smokers compared to current smokers, an effect influenced by the amount of time abstinent from nicotine. Conversely, Neuhaus et al. [52] found ERP evidence that former smoker demonstrated P300 impairment in frontal regions despite an average of 11.9 years of abstinence. Taken together, it is currently unknown if deficits in response inhibition seen in current smokers might recover following long-term abstinence.

To our knowledge, only one study to date has used fMRI to directly investigate response inhibition in individuals who maintained long-term abstinence (i.e., >1 year). Using a difficult Go/No-Go task, Nestor et al. [53] examined neural correlates of response inhibition and error monitoring in current smokers, non-smokers, and former smokers who had at least one year of abstinence prior to study participation (average 7 years of abstinence). In their analysis, only current smokers demonstrated behavioral deficits in response inhibition; however, former smokers were slower overall (significantly slower on both Go trials and error trials compared to never smokers and current smokers). The neuroimaging results showed that, while ever smokers (current smokers and former smokers) demonstrated decreased activation of the inferior frontal gyrus (IFG) compared to never smokers, former smokers demonstrated increased activation of the left anterior cingulate cortex (ACC) for correct response inhibition trials compared to current smokers. Moreover, for errors, former smokers showed an increase in activation of the right middle frontal gyrus compared to both never smokers and current smokers. Interestingly, the fact that ever smokers demonstrated decreased activation of the IFG, a region strongly implicated in inhibitory control of motor responding [54–56] (although see Refs. [57–59] for alternative accounts for the role of the IFG), suggests that there are alternative routes for successful response inhibition and/or compensatory processes might be supported by networks that involve the ACC (e.g., performance or error monitoring [60,61]).

Understanding the mechanisms by which individuals quit smoking or maintain abstinence may be important for developing more effective treatments [62], so it is necessary to explore any subcomponent of response inhibition, including error monitoring, that might support behavior change. Thus, the primary purpose of this study was to investigate response inhibition in current smokers, former smokers and individuals who have never smoked to determine the neural substrates that differ between ever smokers and never smokers, as well as current and former smokers. This is an important question as these differences likely reflect processes that lead to smoking, in addition to offering insight into the mechanisms by which individuals are capable of maintaining long-term abstinence. To do so we measured performance and the BOLD fMRI response in a sample of current smokers, former smokers and never smokers ($n = 126$), while they completed a Go/No-Go task. We hypothesized that the groups would differ on behavioral measures of response inhibition (i.e., current smokers would be slower and/or less accurate on No-Go trials compared to former smokers and never smokers). Additionally, we hypothesized that never smokers would show robust activation differences in brain regions implicated in response inhibition (e.g. IFG, see also regions reported in Ref. [21]) compared to ever smokers, and that former smokers would show increased activation in regions responsible for error monitoring, (e.g., dorsal anterior cingulate cortex, dACC, see also regions identified in Ref. [22]) compared to current smokers and former smokers. Finally, in addition to testing our hypotheses in a relatively novel research population (i.e., former smokers), our design afforded us the opportunity to replicate two larger studies using a similar Go/No-Go task [21,22].

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