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An electrophysiological marker of the desire to quit in smokers

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Abstract

For many smokers, the motivational state of craving is a central feature of their dependence on nicotine, and is often at odds with a general desire to quit. How this desire to quit may influence the craving for a cigarette, however, is unclear. In the current study, we manipulated the level of craving in 24 regular smokers, and recorded EEG measures of brain activity during a rare target detection task utilizing addiction-unrelated stimuli. In response to the non-targets, we observed that smokers wanting to quit showed an enhanced late frontal activation when they were craving vs. not craving, whereas smokers not wanting to quit showed the opposite pattern of activity. A dissociation was also present in the target-related P300 response as a function of craving and desire to quit, with smokers who did not want to quit processing targets differentially between the states of craving and non-craving. The data suggest that distinct top-down control mechanisms during craving may be implemented by people who wish to quit smoking, as compared to those who do not wish to quit. This pattern of findings establishes this ERP activity as a potential biomarker that may help to differentiate people who want to quit their addiction from those who wish to continue to use their substance of choice.

Introduction

When an individual is addicted to a substance such as nicotine, there is often a complex interaction between the learned motivational drive to use the substance (Robinson & Berridge, 1993, 2008), the craving that is associated with that drive (DiFranza & Wellman, 2005), and the desire to stop this behaviour (Smit *et al.*, 2011). Specifically, the maintenance or cessation of addictive behaviour can be thought of as the behavioural outcome of a confluence of factors, with the craving to use and the desire to quit being central to this process, and at odds with each other. Research into addiction has often considered these factors separately, with many studies examining the factors that can modulate craving (e.g., Pripfl *et al.*, 2014) or identifying predictors of successful cessation (e.g., Asmaro *et al.*, 2015). Little is known, however, about how these processes can influence one another in an addict who is currently using, and how this might manifest in patterns of neural activity.

Cessation and craving have been pitted against one another in theories of addiction that posit that there is an imbalance between the top-down, cognitively based, desire to quit (i.e., to inhibit a specific behaviour), and a bottom-up drive or craving for a substance that has been repeatedly associated with reward (Bechara, 2005; Stevens *et al.*, 2014). The cognitive control needed to refrain from using a substance likely involves an interplay of inhibiton-related and attention-related processes, and such executive functions are often associated with a network of frontal-lobe areas that include the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC; see Dosenbach *et al.*, 2008 for review). Indeed, addiction itself is often considered to be a loss of such inhibitory control, leading to the point where substance use is essentially a conditioned (i.e., automatic) response (see Everitt, 2014; for review). Although craving has been associated with reward-related bottom-up processes in regions such as the ventral striatum in humans (e.g., Deserno *et al.*, 2014), there is evidence observed in both rodent models (e.g., West *et al.*, 2014) and humans (Li *et al.*, 2013) that suggests that the frontal lobe may also play a significant role in craving, whether acting independently from, or in concert with, subcortical structures

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(e.g., Franklin *et al.*, 2011). Specifically, work in smokers suggests that the DLPFC and the insula may play key roles in craving, as they have been found to be responsive to subjective craving (Brody *et al.*, 2002), and a lesion present in the insula can substantially diminish the desire to smoke (Naqvi *et al.*, 2007), although its role in smoking addiction appears to be more complex, perhaps due to its heterogeneity (Droutman *et al.*, 2015). It is therefore likely that activity observed in frontal regions may not only reflect effects of craving, but may also be modulated by the desire to quit, perhaps representing a key intersection point of the two opposing forces (Hartwell *et al.*, 2011).

To determine the influence of the desire to quit smoking on craving, we recorded EEG data from smokers across two sessions, one in which they had recently smoked and the other (the craving session) in which they had abstained from smoking for several hours prior to the experiment. The subjects were retrospectively divided into two groups based on their responses to a questionnaire: one group of smokers who wished to quit and one group who had no desire to quit smoking. The task during the EEG session was designed to stir a general awareness of craving/smoking by presenting stimuli that, while not explicitly related to smoking, could purportedly shorten or lengthen the experiment time, thereby potentially bringing the participant closer to or further from the reward of smoking, regardless of task performance. Such stimuli allowed us to examine a neural marker for craving that was independent of cue-induced craving (Sayette *et al.*, 2000), an advantage that allows for the generalizability of this marker across various addictions. We extracted the neural responses [as event-related potentials (ERPs)] to these stimuli across sessions to examine the influence of the intent to quit on extracted craving-related processes.

Based on previous work, we had several predictions as to which components may be modulated by aspects of addiction such as craving. The specific task used was a rare-target detection task, to which subjects only had to make a response about 10% of the time, enabling us to examine the responses to the non-target stimuli (standards) without any contamination from motor-related activity, while still having the target-related responses present on a small percentage of trials. In response to the target stimuli, we predicted to see that the P300 component, previously observed to be insensitive to the probability of a reward in addicts (Morie *et al.*, 2016), would not be sensitive to the task conditions (purportedly bringing participants closer to or farther away from their reward of smoking), but might rather show an enhancement in the craving condition during which overall arousal may have been higher (Donohue *et al.*, 2016). In response to the standard stimuli, we expected to see a frontal component similar to a cue-related negativity (Morie *et al.*, 2014, 2016), with such a negative process likely having an extended duration, as has been observed in addicts in a response to substance-related cues (Littel *et al.*, 2012) that likely induce craving (Carter & Tiffany, 1999). Because craving processes are in conflict with the desire to quit, we expected that this frontal component may exhibit a different pattern of activity (i.e., top-down control) in response to craving for smokers who wished to quit as compared to those who did not wish to quit.

Materials and methods

Participants

Twenty-four habitual smokers took part in this study (age range 18–33, mean = 25.5, nine female, all right-handed). Six additional participants were excluded from the final analysis due to excessive physiological artefacts in at least 40% of the trials in one or more of the sessions. Participants were recruited on the basis of smoking regularly. Any other questions about their smoking habits, including whether or not they wished to quit, were asked later through a questionnaire and were not mentioned during the recruitment process in order to avoid any bias. All participants had smoked regularly for at least 1.5 years, with 19 years being the longest reported period as a regular smoker (mean = 8.67 years), and they smoked an average of 14.7 cigarettes/day (range of 7–32.5). Of the 24 participants, 16 reported wanting to quit smoking, and eight reported not wanting to quit, and the participants were grouped according to this desire to quit in the analysis. From the 16 participants who currently wanted to quit smoking, 14 had previously tried to quit on one or more occasions. From the eight participants who currently did not want to quit smoking, four had previously tried to quit, but, at the time of the experiment, they no longer wished to quit. Participants were compensated for their time at a rate of 6 Euros per hour. All participants gave written, informed consent, and the Medical Ethics Commission of the Otto-von-Guericke University, Magdeburg approved all methods and procedures, which were carried out in accordance of the Declaration of Helsinki.

Craving manipulation

Each participant completed two separate measurement sessions, one immediately after having smoked, and the other while in a nicotine-deprived 'craving' state. For the time leading up to the appointments, participants were instructed to smoke as they typically would. On the day of the non-craving session, participants smoked a cigarette immediately prior to the start of the EEG procedure. If they had not reported smoking on their walk to the building, they were instructed to smoke before we began any part of any session. On the day of the craving session, participants came to the clinic three hours prior to the start of the EEG session. The craving and non-craving sessions always took place on different days. For the non-craving session, from the arrival time until the collection of the EEG data, each participant was closely monitored to ensure he/she did not smoke. During the wait period, participants remained in view of one or more experimenters in a shared office space to ensure compliance with the non-smoking protocol. Half of the participants completed the craving session first, and the other half completed the non-craving session first, with the order of the sessions randomly assigned across participants. Of note, the sessions were also counterbalanced within the subgroups of participants who wished to quit and those who did not wish to quit.

Stimuli and task

In both sessions, participants completed a rare-target detection task within a prospective delay paradigm. The visual stimuli consisted of images from three different object categories. The categories were furniture, clothing, and kitchen utensils, and each category was comprised of 24 representative images. The images were equated for luminance across categories, and were all presented in grey-scale on a white background. Each image subtended 6.75 by 6.75 degrees of visual angle and was presented at fixation for 1200 ms, followed by a jittered ITI between 800 and 1400 ms (see Fig. 1). The stimuli were presented using PRESENTATION software (Neurobehavioral Systems, Albany, CA, USA). Three images in total (one image from each object category) were selected for each given participant to be the target images. Upon presentation of one of these images, participants were instructed to respond via button press on a keyboard

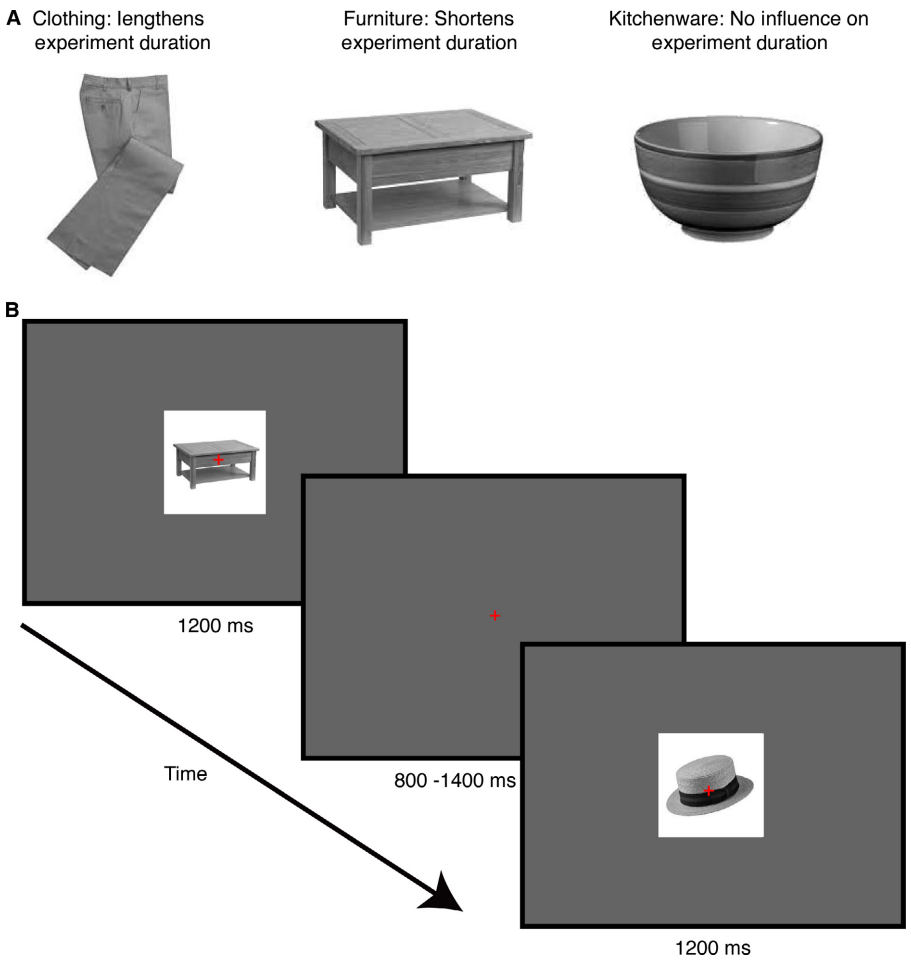

FIG. 1. Task. (A) Representative images from the three categories of objects used in the experiment. Each participant was randomly assigned a category that could (ostensibly) make the experiment longer (here, clothing), shorter (here, furniture), or have no influence on session duration (here, kitchenware). (B) The task was a rare-target detection task, with singularly presented images followed by a jittered ITI. Ten percent of the trials contained target objects, for which the participant had to respond via button press.

with the right hand. Targets were rare (~ 10% of the trials) and were the same across craving and non-craving sessions for a given participant. Across participants, the specific items from each category identified as targets were randomly assigned such that each of the 24 images in each category was a target for one of the 24 participants.

The remaining ~ 90% of images that were non-targets (standard images, no response required) were randomly presented, drawn from each represented category. Each participant was told at the start of the experiment that each category of images had a different effect on the total experimental session duration. Specifically, images from one category of items (standards and target), when presented, would lengthen the session by a random period of time (as determined by the computer), whereas items from another category would shorten the session in a similar manner, and the third would have no effect on the length of the session. For example, a particular participant might be told that furniture would lengthen the experiment, clothing would shorten it and kitchen utensils would have no effect. These conditions are subsequently termed here as longer, shorter, and neutral. The order of these assignments was randomized and counterbalanced across participants. Contrary with what participants were told, however, all sessions entailed a consistent number of trials (869), and the experiment duration was held constant (~ 35 min). In order to bolster the illusion that participants were actually participating in an experiment that could be variable in time, the total number of trials was deliberately not made to be a 'round' number by having an occasional trial be omitted from one category, thereby making the number of trials slightly variable while still having essentially equivalent numbers of trials across all categories. (In other words, the initial trial percentages of 10% targets and 90% non-targets were generated from a basis of 900 trials, but, at random, 31 trials were omitted from presentation, leaving 869 total trials and the ratio of 90% non-targets to 10% targets approximate.) This was also done in the event the participants were counting the number of trials they had been presented within each category. Debriefing suggested that no participant had done this and also confirmed that the instructions and the highly variable amount of jitter reinforced the belief of participants that the images were influencing the duration of the experiment.

Questionnaires

To assess the level of addiction, participants completed the Fagerström Test for Nicotine Dependence (FTND; Heatherton *et al.*, 1991). Craving was assessed in both sessions immediately prior to the collection of the neural data (as the EEG cap was being applied). The questionnaire used to determine the level of craving was the Questionnaire on Smoking Urges (QSU; Müller *et al.*, 2001; Tiffany & Drobes, 1991). From this questionnaire, the scores

on two factors relating to craving can be obtained, the first assessing positive symptoms such as the 'desire and intention to smoke with an anticipation of pleasure from smoking' and the second assessing negative symptoms such as 'the relief from nicotine withdrawal or the negative affect associated with an urgent and overwhelming desire to smoke.' Participants also filled out a brief questionnaire, from which more detailed information on their smoking history and desire to quit was obtained. The questions on this questionnaire included the following: 'On average, how many cigarettes do you smoke per day?' and 'How many years have you regularly smoked?' and 'Would you like to quit smoking?' and 'Have you ever tried to quit smoking? If yes, how long were you successful?' and 'Do you enjoy smoking?' All questionnaires were administered in German, which was the native language of all participants with the exception of one participant for whom the questionnaires were administered in English, as he was not fluent in German.

EEG acquisition and analysis

EEG data were continuously recorded in an electrically shielded chamber using a 32-Channel ActiChamp System with an ACTICAP and VISION RECORDER software (Brain Products Inc., Gliching, Germany). The sampling rate for recording was 500 Hz per channel. The data were referenced online to the right mastoid and impedances were kept below 5 kΩ. For analysis, the data were processed using the Matlab-based EEGLab and ERPLab toolboxes (Delorme & Makeig, 2004; Lopez-Calderon & Luck, 2014). Offline, the data were epoched from 500 ms pre-stimulus to 1500 ms post-stimulus. Such a long time period was used in order to ensure that we would capture the entire period of activation of any slow-wave frontal components as well as the P300, should it take a long period of time to return to baseline. Trials in which a false-alarm occurred after a non-target was presented and trials for which no response was given for a target were eliminated from further analysis. Artefacts were rejected using a peak-to-peak amplitude threshold-based method, with the threshold being adjusted for each participant for maximal sensitivity (i.e., to remove the most blinks and physiological noise) and selectivity (i.e., keeping the number of usable trials as large as possible). This was done in an iterative manner in which the threshold would be increased or decreased (dependent on if artefacts were being accepted and/or artefact-free trials were being rejected), and then the data would be visually inspected to ensure that the data were free from blinks and other large artefacts. The artefact rejection process was blind to session and condition, and ultimately led to a slightly higher percentage of epochs being removed from the craving non-target trials (M = 21.5%) than from the non-craving non-target trials (M = 18.1%; $t(23) = 2.49$, $P = 0.02$). For the target trials, the artefact rejection rates did not differ across sessions, with the craving session having an average of 15.8% of trials rejected and the non-craving session having 13.4% of trials rejected
($t(23) = 1.45$, $P = 0.16$). This left a total of, on average, of 626 trials in the non-target condition across sessions (range: 460–768), and a total of, on average, 76 trials in the target condition (range: 52–88). The remaining artefact-free epochs were re-referenced to the algebraic average of the left and right mastoids, filtered with a low pass 30 Hz filter, and selectively averaged for each condition and session to generate the ERP waveforms. For plotting and statistics, the data were baseline corrected from −200 to 0 ms.

Statistical analysis was conducted over two time periods for the targets and for the standards. For the standards (collapsed across conditions and sessions), a broad frontal negativity was observed. This negativity was measured from 200 to 700 ms, averaged across a frontal ROI: Fz, F3, F4, Fp1, Fp2. For the targets, we measured the mean amplitude across condition and session at sites Pz and Cz from 400 to 800 ms, a time period that captured the P300 response. The mean amplitude data were then submitted to a repeated-measures ANOVA, with the factors of craving (craving, non-craving), delay condition (longer, shorter, neutral) and the between-subjects factor of desire to quit (yes, no). All values reported are Greenhouse-Geisser corrected, and the alpha level of significance was set at 0.05.

Results

Questionnaires

Participants scored a mean of 3.79 (classified as low smoking) on the FTND level-of-addiction questionnaire, with the range falling between 0 (very low) and 8 (high). To assess the craving manipulation as measured by the QSU, we ran a repeated measures ANOVA with the factors of craving (craving, non-craving), and the between-subjects factor of expressing an interest in quitting (yes, no). This revealed a significant main effect of craving for both the first (positive) factor (Mean Craving = 5.54, SD = 1.13; Mean Non-Craving = 3.86, SD = 1.38; $F_{1,22} = 42.9$, $P < 0.001$, $\eta_P^2 = 0.66$) and the second (negative) factor (Mean Craving = 3.35, SD = 1.36; Mean Non-Craving = 1.97, SD = 1.05; $F_{1,22} = 31.4$, $P < 0.001$, $\eta_P^2 = 0.59$). For both factors in the QSU, no main effects of quitting were present, and quitting and craving did not interact significantly, suggesting that the QSU was not sensitive to any effect the desire to quit may have had on craving.

Behaviour

For the target trials, accuracy and response time (RT) measures were collected across sessions. Participants were highly accurate at responding to the presence of a target (M = 99.2%). The percent correct data were entered into a repeated-measures ANOVA with the factors of craving (craving, non-craving), delay condition (longer, shorter, neutral), and the between-subjects factor of desire to quit (yes, no). No main effects or interactions were observed for the accuracy data (all P's > 0.1). The RT data were entered into an ANOVA with the same factors as the accuracy data, again resulting in no significant main effects or interactions. Here, however, there was a trending effect of craving (Mean Non-Craving RT = 619 ms, Mean Craving RT = 605 ms; $F_{1,22} = 3.71$, $P = 0.07$, $\eta_P^2 = 0.14$), with participants tending to respond more rapidly in the craving session. Finally, the false alarm rate to the non-target stimuli (0.08% of total standard trials) was entered into an ANOVA with the same factors as above, again revealing no main effects or interactions (all P's > 0.1). In summary, the desire to quit and the craving manipulation did not influence the accuracy and false-alarm rate on this rare-target detection task. Craving did, however have the tendency to speed-up the RTs, perhaps indicating the presence of a more aroused state associated with an increased desire to smoke.

EEG

Responses to standards (non-targets)

The neural response to the standards included a predominant frontal-central negativity. A repeated-measures ANOVA on the mean amplitude of this effect during the 200–700 ms post-stimulus time

window with the factors of craving (craving, non-craving), delay condition (longer, shorter, neutral), and the between-subjects factor of expressed interest in quitting (yes, no) showed a significant interaction between craving and quitting interest ($F_{1,22}$ = 11.63, P = 0.003, η_P^2 = 0.35), with no other main effects or interactions reaching significance. This interaction was driven by a reversal in the pattern of frontal activation under a condition of craving and as a function of quitting. Specifically, the participants who wanted to quit showed a frontal response that was more negative (i.e., greater) for craving vs. non-craving conditions (t(15) = 2.64, P = 0.02). In contrast, the participants who had not expressed interest in quitting showed a more negative amplitude (i.e., greater) for non-craving vs. craving
(t(7) = 2.34, P = 0.05). Indeed, whether or not a smoker wanted to quit led to a reversal of the frontal response during this time period as a function of craving. Figure 2 presents this novel electrophysiological marker, where the reversal in activity as a function of craving can be seen in the waveforms and the bar graph of the mean amplitudes.

Responses to targets

A repeated-measures ANOVA on the P300 response to the target stimuli was run using the factors of craving (craving, non-craving), delay condition (longer, shorter, neutral), and the between-subjects factor of expressed quitting interest (yes, no). This showed a main effect of craving ($F_{1,22}$ = 5.14, P = 0.03, η_P^2 = 0.19), a significant craving × quitting interaction ($F_{1,22}$ = 7.22, P = 0.01, η_P^2 = 0.25), and a marginal condition by quitting interaction ($F_{1,22}$ = 3.39, P = 0.05, η_P^2 = 0.13). The craving by quitting interaction was driven by a significant difference in the P300 for the group that did not want to quit as a function of craving (t(7) = 3.95, P = 0.006). The quitting by condition interaction was driven by a trend for the differential processing of the shorter and neutral conditions (t(7) = 2.12, P = 0.07). Figure 3 summarizes these results, showing the influence of both craving and quitting on target processing.

Discussion

Although some might consider the persistence of addiction an automatic process, with the craving that drives the next consumption to be a habitual, routine phenomenon, here we demonstrate that the neural responses characteristic of a craving state differ across participants in a manner that is directly linked with the desire to quit, specifically the unprompted expressed desire to quit. Using a rare-target detection task designed to make participants continually aware of when they would next be able to smoke, in conjunction with a two-session structure manipulating the level of craving for cigarettes, we investigated the interactions of craving, the expressed desire to quit, and the processing of stimuli that would either bring the subject closer to, or further from, their next cigarette. In response to the standard (non-target) stimuli, participants who wished to quit smoking showed an enhanced late frontal response when they were craving as compared to non-craving, whereas participants who did not wish to quit showed the opposite pattern of frontal activity. Furthermore, target-related responses were modulated by craving and intent to quit, with quitting also influencing the neural response to the different task conditions ostensibly affecting the time until the 'reward' of smoking. Together, the distribution and timing of these effects indicate that the wish to quit smoking acts in a top-down manner to modulate the brain's response to stimuli under varying conditions of craving.

The frontal effect elicited in response to the standards was both quite anterior and relatively late in time, starting around 200 ms post stimulus onset. This indicates both that this effect was not related to any early sensory (or early attentional) processing (Hillyard *et al.*, 1998), but more likely a marker of sustained attention (Chao *et al.*, 1995) or top-down cognitive control (Eimer, 1993). The reversal of the response to craving as a function of quitting further suggests that a given individual's attitude toward their addiction can strongly influence the cognitive processing that occurs during craving. Indeed, factors that can be related to an individual's attitude, such as impulsivity, have been shown to influence inhibition-related activity patterns in abstinent substance users (Bell *et al.*, 2014), with the current data supporting such findings of differential top-down control across substance users. It is also possible that the pattern of activity observed here may reflect a type of conflict (e.g., simultaneously craving a cigarette due to being deprived of smoking and wanting to quit smoking) as activity from the anterior cingulate cortex (ACC) has been shown to have a similar frontal distribution and is related to conflict detection (Liotti *et al.*, 2000; van Veen & Carter, 2002). Although previous fMRI studies have observed neural markers in the ACC and insula that correlate with success in quitting (e.g., Janes *et al.*, 2010; Versace *et al.*, 2014), the pattern observed here appears to reflect the requisite desire to quit, with the ultimate outcome of the success of quitting unknown.

Target-related effects showing an interaction between quitting desire and craving, albeit with a different pattern than for non-

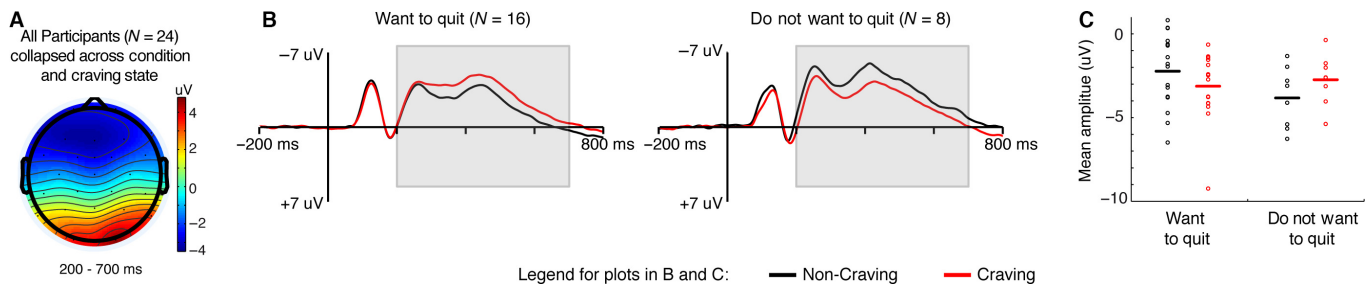

FIG. 2. Frontal effect of craving and desire to quit. (A) Topographic distribution of the frontal slow-wave effect shown from 200 to 700 ms. Topomap includes data from all 24 participants and is collapsed across the delay conditions as well as the craving state. (B) ERP traces averaged across frontal sites Fz, Fp1, Fp2, F3 and F4, collapsed across experimental conditions for trials with standard (non-target) stimuli only. The traces, plotted separately for the participants who reported wanting to quit and those who reported not wanting to quit, reveal a distinct pattern of neural activity as a function of craving. The grey area highlighted is the time window (200–700 ms) for which the effect was statistically tested. (C) Scatter plots of the mean ERP amplitudes shown in A, averaged across 200–700 ms. The data are plotted with the participants divided as a function of their desire to quit, with each dot representing the mean amplitude value for the non-craving (black) and craving (red) condition for a given participant. The thick horizontal lines represent the mean for each condition and group. The craving and non-craving activity significantly differed for both the participants who wanted to quit and also for those who did not wish to quit.

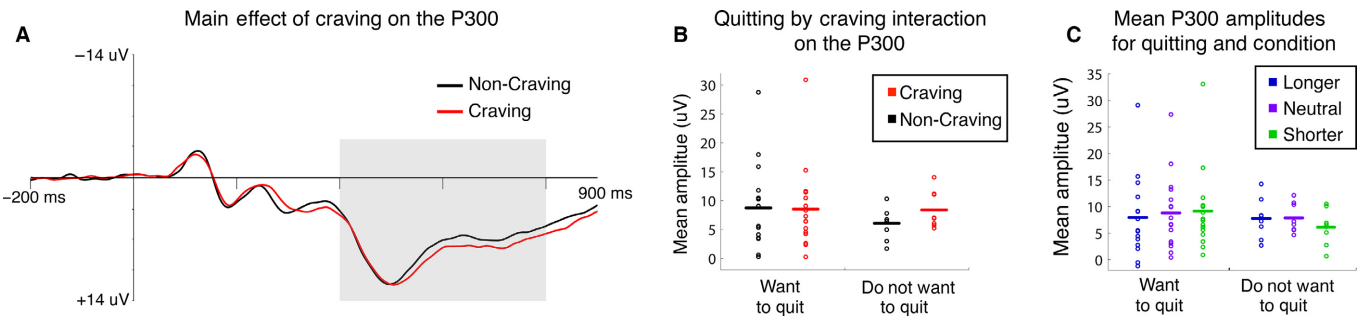

FIG. 3. Target-related processing. (A) ERP traces of the P300 (at an average of sites Cz and Pz) showing the main effect of craving, collapsed across condition and across desire to quit. Grey area shows the 400–800 ms time window, which was tested for statistical significance. (B) Scatter plot of mean amplitudes of the P300 (same sites and time window as highlighted in A). The data are plotted with the participants divided as a function of their desire to quit, with each dot representing the mean amplitude value for the non-craving (black) and craving (red) condition. The thick horizontal lines represent the mean across that group of participants and condition. A significant difference was observed in the participants who did not want to quit between the craving and non-craving P300 amplitude. (C) Scatter plot of mean amplitudes of the P300 (same sites and time window as highlighted in A) depicting the condition by desire to quit. The data from each participant is plotted as a function of group (wanting to quit, not wanting to quit) and the mean amplitude of the P300 by condition. The thick lines represent the mean values for the condition/group.

targets, were also observed. Specifically the target-detection-related P300 response was enhanced in participants who did not wish to quit when they were craving, and diminished when they were not craving, a pattern that was not present in the group who wished to quit. Given that P300 amplitudes can be modulated by attention (Polich, 2007), it is likely that the state of craving coopts the attention of those subjects who have no desire to quit, resulting in the enhanced P300 responses overall. Although it was somewhat surprising that there were no effects of condition in response to the standards, and the interaction between condition and quitting for the targets was only a trend, it is perhaps the case that the influence of the task conditions themselves was relatively weak in comparison to the more global factors of craving and quitting.

Together, these findings suggest that late stimulus processing can vary across states of craving, and such variation is modulated by the intention to quit. This modulation of both a frontal ERP signal and a parietal target-related attentional processing signal is consistent with the notion of top-down control being important for the cessation of addiction (Garavan & Weierstall, 2012). The flip observed across conditions of craving as a function of wanting to quit suggests that smokers with a genuine interest in quitting approach the state of craving a cigarette in a different way from those who do not wish to quit. Our choice in the present study to not use smoking-related stimuli differs from the widely-employed approach of using cue-induced craving in both behavioural (e.g., Erblich & Michalowski, 2015) and neural (e.g., Moran-Santa Maria *et al.*, 2014) studies. By eliminating such cues, our data speak to the more general phenomenon of craving as a motivational state, rather than the increased desire to smoke in response to seeing a smoking-related cue (Carter & Tiffany, 1999). Both cue-induced craving and non-cue-induced craving are important features of addiction, and by tapping into the more general state of craving, the current paradigm could assess frontal activity that likely occurs frequently under real-life settings where the desire to smoke is triggered by an internal state rather than some external, smoking-related cue, such as seeing another person smoke or seeing a lighter.

Several key points about the current experiment should be noted. First, participants were not recruited based on whether or not they wished to quit, and his/her interest in quitting was one of a series of many questions each participant received. As such, although an individual participant was intrinsically aware of whether or not they wished to maintain the habit of smoking, he/she had no reason to assume that this was relevant to the experiment. Therefore, the effects we observed here were likely not induced by the participants wanting to behave in a certain way, or trying to meet any sort of experimenter demand. Second, of the participants who said that they wished to quit, none had a concrete plan of quitting immediately after the experiment, suggesting that this desire was more an abstract wish than a plan on which they would immediately act. This implies both that this dissociation as a function of craving is a very general 'cognitive attitude' and perhaps an even stronger effect might be found in participants who had concrete plans to quit immediately following the experiment. Finally, the questionnaire measures of craving were not sensitive to the desire to quit, suggesting that the neural marker we observed may be a more sensitive measure or taps into a different process of craving than the questionnaire.

One limitation in the current study is the small sample size, particularly of the participants who did not wish to quit (n = 8). Because we were not recruiting participants based on their interest in quitting (i.e., we did not wish to inadvertently induce any experimental demand characteristics by telling people they were participating because they did or did not want to quit smoking), our sample sizes ended up as large as they were due to chance. The baseline in the ERP data is quite clean, however, for the eight participants, suggesting that the signal-to-noise ratio is still quite good for this group. That said, these findings should be replicated in a larger sample to ensure that they would hold across a population. Another point worth noting is that within our sample of smokers, there was a large variability in the amount smoked (7–32.5 cigarettes/day). This amount did not show any significant correlation (post hoc) with any of our neural measures, but it is still possible that such variability in the amount smoked would have influenced our results in a manner to which a simple correlational analysis were not sensitive.

To summarize, we observed a novel electrophysiological marker of the desire to quit that was modulated by a participant's state of craving. This was apparent primarily in a late frontal negativity to all the non-target stimuli, but also present in the target processing reflected in the P300. Such an objective neural marker thus offers the potential to be used as an indicator of a participant's desire to quit, which could be of potential value in treatment centres, and represents yet another factor, previously unobserved, among the constellation of forces that contribute to the maintenance or cessation of addictive behaviour. As this electrophysiological dissociation appeared to be fairly robust in the current data, this bolsters the likelihood that this pattern might be stronger under various settings where quitting was more imminent. Both the cost-effectiveness of

this neural measure (in comparison to MRI) and the relative ease with which EEG data can be acquired, suggests promising applicability of these findings. This result also opens up the possibility for future work to explore the robustness of this marker across different substances of abuse, relative levels of craving, proximity to a quit date, and success of quitting.

Author contributions

SED, JAH and MAS designed the study. SED collected the data. SED analysed the data. SED, JAH, HJH, MGW and MAS wrote the manuscript.

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