ORIGINAL ARTICLE

People with tobacco use disorder exhibit more prefrontal activity during preparatory control but reduced anterior cingulate activity during reactive control

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Abstract

Reduced inhibitory control and a hypersensitivity to reward are key deficits in drug dependents; however, they tend to be studied in isolation. Here, we seek to understand the neural processes underlying control over reward and how this is different in people with a tobacco use disorder (pTUD). A novel variant of the monetary incentive delay task was performed by pTUD ($n = 20$) and non-smokers ($n = 20$), where we added a stop-signal component such that participants had to inhibit prepotent responses to earn a larger monetary reward. Brain activity was recorded using functional magnetic resonance imaging (fMRI). We estimated stop signal reaction times (SSRTs), an indicator of impulsivity, and correlated these with brain activity. Inhibitory accuracy scores did not differ between the control group and pTUD. However, pTUD had slower SSRTs, suggesting that they may find it harder to inhibit responses. Brain data revealed that pTUD had greater preparatory control activity in the middle frontal gyrus and inferior frontal gyrus prior to successful inhibitions over reward. In contrast, non-smokers had greater reactive control associated with more activity in the anterior cingulate cortex during these successful inhibitions. SSRT–brain activity correlations revealed that pTUD engaged more control-related prefrontal brain regions when SSRTs are slower. Overall, while the inhibition accuracy scores were similar between groups, differential neural processes and strategies were used to successfully inhibit a prepotent response. The findings suggest that increasing preparatory control in pTUD may be one possible treatment target in order to increase inhibitory control over reward.

KEYWORDS

anterior cingulate cortex, inhibitory control, nicotine use disorder, prefrontal cortex, striatum

1 | INTRODUCTION

Addiction is a complex disorder that includes multiple decision-making symptoms.[1] Key deficits include hypersensitivity towards drug-related rewards[2] and reduced inhibitory control.[3] These deficits may

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contribute to the high persistence in drug-seeking behaviours and impulsive decision making found in people with a substance use disorder (pSUD). Impulsivity is defined here as overvaluing a smaller immediate drug reward compared with the larger later reward of better health from abstinence.[4] A better understanding of these processes may offer insight into ways of decreasing drug-seeking behaviours and avoiding relapse by exercising control over immediate rewards. These differential processes of inhibiting a response and the hypersensitivity to rewards have been relatively well studied but are typically studied independently.

The stop-signal task is commonly used to study processes involved in response inhibition.[5] In this task, there is a prepotent tendency to respond to a target stimulus due to the frequent 'go trials'. However, less frequently, there is a stop signal presented with a short latency to the target stimulus, where individuals now need to withhold their response. These are termed 'stop trials'. The dorsolateral prefrontal cortex (dlPFC), including the inferior frontal gyrus (IFG), is associated with successfully inhibiting a response during stop trials,[6] both, prior to inhibition (preparatory control[7,8]) and during inhibition (reactive control[9]). Those with a SUD, including to nicotine, have demonstrated reduced inhibitory control in this stop-signal task,[10–12] and this has been associated with hypoactivity in regions within the PFC.[13]

The mechanisms underlying reward processing have been studied through various paradigms, including the monetary incentive delay (MID) task.[14] The MID task cues participants on possible upcoming rewards and then asks them to respond to a target stimulus to win or lose rewards—depending on the variant of the task used. The striatum has typically been associated with reward processing,[15] and in this MID task, increased striatal activation has been associated with reward anticipation.[16] Administering the MID task to participants with a SUD has identified aberrant striatal functioning (with increases and decreases relative to controls), particularly when they are asked to anticipate rewards. This aberrant striatal functioning is thought to contribute to the heightened impulsivity and impaired reward processing,[17] and although the opponent-process theory[18] suggests that this striatal aberration is a possible predictor of developing addictive-like behaviours, evidence supporting this relationship is mixed.[19,20] Lastly, PFC hypoactivation during reward processing is also found in pSUD, implying that there may be reduced inhibitory control over choices with immediate rewards.[21]

Taken together, the PFC appears to increase cognitive control, and the striatum plays a role in processing and anticipating rewards. Both brain regions exhibit aberrant functioning in addiction and possibly contribute to the reduced inhibitory control over immediate reward which may drive impulsive decision making. However, the neural mechanisms underlying how the two processes interact remain less clear. Namely, how does the brain exercise inhibitory control over reward in pSUD? Is this through modulation of PFC activity, striatal activity, or both? We hypothesized that reduced PFC activity may be associated with failed inhibitions, consistent with its role in cognitive control. We further hypothesized that increased striatal activity may also be associated with failed inhibitions, by possibly anticipating and overvaluing the smaller sooner rewards.

To investigate this question, we used a novel variant of the MID task—termed monetary incentive control task (MICT). Here, we added the stop-signal component to the MID task. We also used real monetary reward components of two modalities: smaller sooner and larger later. To win the smaller reward, participants had to quickly respond to a target stimulus. To win the larger reward, participants had to successfully inhibit their response on most of the stop trials. If participants responded quickly on stop trials, they still won the small reward. Previous studies[22,23] have also combined the stop-signal task with a reward manipulation; however, a critical distinction is that in our task, there is also a reward given for failing to inhibit, whereas reward was only given for successfully inhibiting in the previous tasks. Failed inhibition was rewarded to better simulate real-world abstinence where failing to inhibit comes with a small immediate reward. Importantly, participants were not updated on their progress towards winning the larger reward, because again, the aim was to simulate real-world abstinence and attempting abstinence does not come with the immediate certainty of the receipt of a larger reward (better health in the future). However, a relapse comes with the more certain small reward (drug).

Previous accounts have found that monetary incentives can (1) increase reactive control in the stop-signal task by increasing engagement of control-related PFC activity[24]; (2) reduce conflict during a conflict-response task, associated with increased functional connectivity between intraparietal sulcus and the striatum, engaging more top-down control[25]; and (3) increase performance in the Stroop task in both healthy controls (by enhancing dorsolateral PFC activity) and in people with a cocaine use disorder (by enhancing occipital lobe activity and the functional connectivity between the dorsolateral PFC and striatum).[26] In contrast, our task provides a smaller sooner incentive for failed inhibitions (to better simulate real-world abstinence), and accordingly, we hypothesized that this may make inhibitions more difficult by engaging striatal anticipatory activity, particularly in pSUD, and successful inhibitions may require increased PFC engagement, especially to exercise control over the smaller sooner incentive for failed inhibitions. There was also a manipulation where participants were cued on the probability that the upcoming trial would be a 'stop' trial. This manipulation was used to investigate the potential interaction between reward anticipation and 'stop' difficulty, with a higher probability condition hypothesized to engage control-related PFC regions and a higher stop accuracy score.

We recorded brain activity using functional magnetic resonance imaging (fMRI) while participants performed this task. Both groups of people with a tobacco use disorder (pTUD) and non-smokers healthy controls underwent this task. Nicotine withdrawal can produce neurotoxic effects in the mesolimbic reward systems comparable with other drugs of abuse including amphetamine, cocaine and opiates.[27] We also estimated stop signal reaction times (SSRTs), which is a measure of how effortful it is to inhibit a response, as well as an index of impulsivity.[28] Overall, we investigated how the brain may exercise control over smaller sooner rewards to attain a larger later reward in pTUD and non-smokers.

2 | MATERIALS AND METHODS

2.1 | Participants

Participants were recruited through advertisements at the University of Melbourne and through a community website. All participants provided written informed consent that was approved by Human Ethics Committee of the University of Melbourne and the Royal Children's Hospital. The pTUD group consisted of 20 individuals (10 males, 10 females; mean age = 24.3 years, standard deviation = 4.7, range = 18–34). The brain structural images for one pTUD group participant were not retrievable; hence, brain imaging data for this participant were not analysed. The control group consisted of twenty non-smokers (10 males, 10 females; mean age = 23.7 years, standard deviation = 4.3, range = 18–32). One participant in the control group had an anatomical anomaly; however, this was very minor, and the participant was included in the analysis. All participants were right handed—determined by the Edinburgh Handedness Inventory.[29] Participants in the control group had smoked less than six cigarettes in their lifetime. Participants in the pTUD group smoked at least 15 cigarettes daily, and the average Fagerström Test for Nicotine Dependence (FTND) score was 3.95, indicating close to moderate dependence.[30] The group average for years of cigarettes smoked was 7.6 years.

Prior to the experiment, the pTUD group had been abstinent for at least 3 h. This was confirmed by both a self-report and the carbon monoxide breath measure. Exclusion criteria for both groups consisted of a history of neurological or psychiatric disorder, current use of psychotropic medication (other than nicotine for the pTUD group). Scanning data were collected between 9 AM and 5 PM across participants, and they were advised not to binge prior to abstaining for the 3 h. Participants also arrived at least 1 h prior to scanning for task preparation/practice, which also prevented them from smoking. The 3-h abstinence window was chosen due to nicotine's half-life of approximately 2 h,[31] and data suggesting that 3-h abstinence did not produce withdrawal effects on cognition.[12]

### 2.2 | MICT behavioural paradigm

The MICT paradigm is a modified version of the MID task but with the addition of a stop-signal component (see Figures 1 and 2). Each trial began with a cue symbol, presented for 2 s. The cue was used to inform participants on the probability that the upcoming trial was a stop trial and whether it is a reward or a neutral trial. Following this cue epoch, there was a variable delay presented for 2–4 s, with 1-s jitter. This delay period was termed the anticipation epoch and composed of a blank screen. After this, the target was presented. This was either an 'X' or an 'O', presented for 400 ms, with a blank screen for 600 ms following this. Participants had to press the correct button (left or right) associated with the target letter within 400 ms to get the small 20¢ reward, if this was a reward trial. For stop trials, a square border around the target letter would appear after 150 ms latency. If this stop trial was a reward trial and participants withheld their response at 60% or more of these rewarding stop trials, they would get the large $20 reward at the end of the task. If they responded within 400 ms to the rewarding stop trial, they would still get the small 20¢ reward. For neutral trials, no monetary reward could be received, irrespective of performance. Overall, there were four conditions based on the following trial types: (1) reward trial with 20% probability (R20), (2) neutral trial with 20% probability (N20), (3) reward trial with 40% probability (R40) and (4) neutral trial with 40% probability (N40). These could all be either 'go' or 'stop' trial types. Following the trial, participants were presented with feedback for 1.5 s. The feedback indicated their performance and if they had won the small 20¢ reward (see Figures 1 and 2). Following each run of trials, participants were given feedback on how much money they had earned from go trials. However, importantly, feedback on stop trial accuracy and any associated monetary gain on the larger $20 reward was not provided until the end of the task.

There was a total of 216 trials, with 54 of these being stop trials (25%). This different allocation of 'stop' and 'go' trials (25% stop trials and 75% go trials) is commonly used to create the prepotent tendency to respond in the stop-signal paradigm.[5] The task was split into six runs, with 36 trials per run. Trials were presented in a pseudorandom, intermixed design, within each run. The R20 condition had a total of 78 go trials and 18 stop trials, R40 had 30 go trials and 18 stop trials, N20 39 go trials and 9 stop trials and N40 had 15 go trials and 9 stop trials. The task lasted approximately 45 min including rest breaks between runs. Please see the Supporting Information for (1) the apparatus details, (2) experimental procedure, (3) MRI sequences used and (4) the methods of SSRT estimation.

2.3 | Behavioural analysis

For performance indices, we used stop-accuracy percentage (calculated as the number of stop trials where participants inhibited their responses divided by the total number of stop trials) and go-accuracy percentages (calculated as the number of responses made on go trials in under 400 ms divided by the total number of go trials). Data above and/or below three standard deviations from the mean were removed as outliers. To test for significance, we used repeated-measures analysis of variance (ANOVA). There were three factors and each factor had two levels (2 × 2 × 2 ANOVA design). These included (1) factor of probability, with levels of low (20%) and high (40%) probabilities; (2) factor of reward, with levels of rewarding trial and neutral trial; and (3) factor of group, with levels of pTUD group and control group. To test for simple effects, independent t tests were conducted where ANOVA yielded significant results, corrected for multiple comparisons using Šidák correction. The partial eta-squared (η_p^2) was calculated as a measure of effect size with 0.01 being small, 0.06 being medium and 0.14 being large.

(A)

(B)
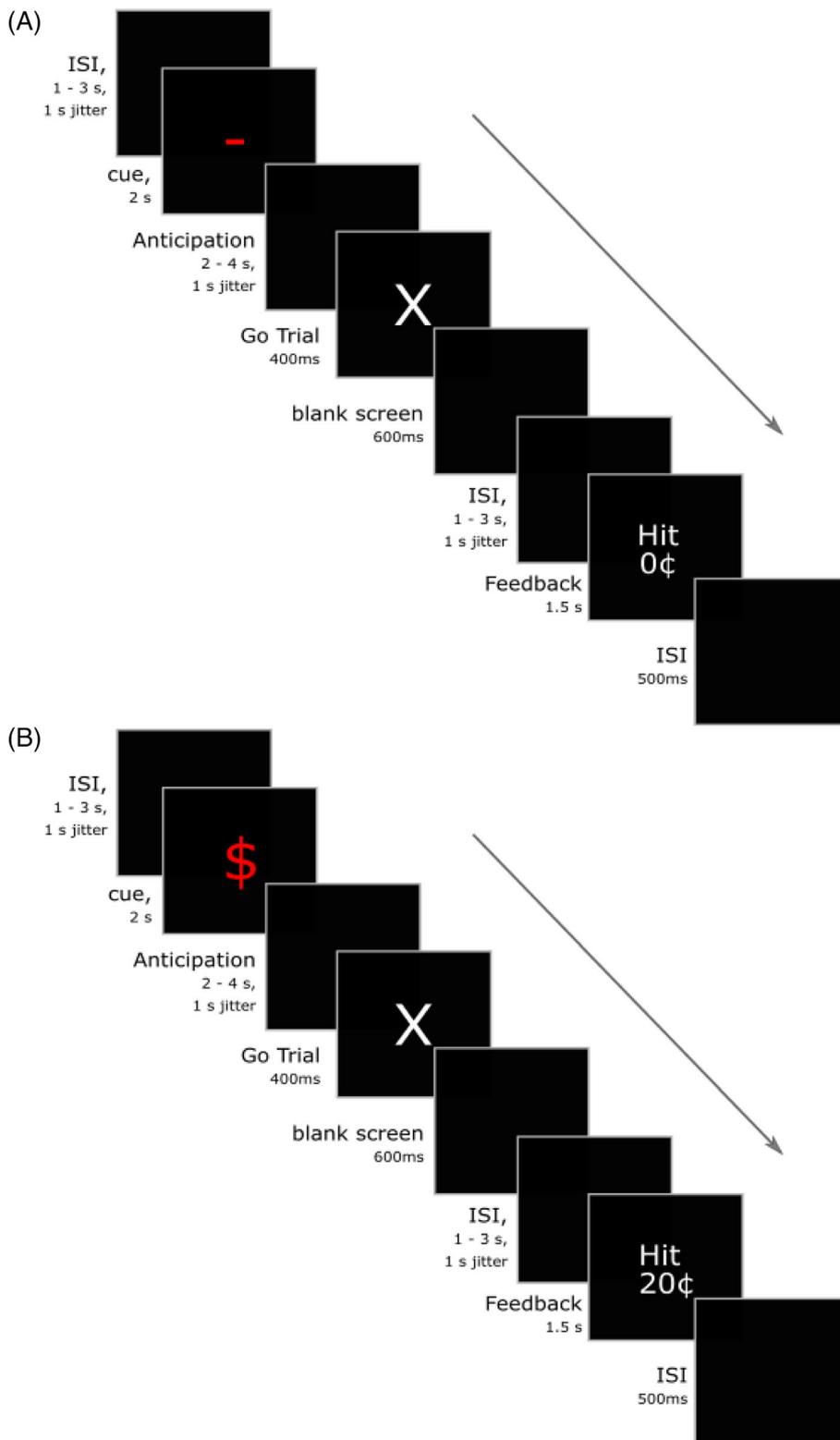
FIGURE 1 Example sequences of go trials. If the cue symbol was a dash ('-'), the upcoming trial was a neutral trial and no money could be won, irrespective of performance. If it was a dollar symbol ('$'), the upcoming trial would be a reward trial where monetary rewards could be won, depending on performance. If the colour of the symbol was white, there was a 20% probability that the upcoming trial would be a stop trial. If this colour was red, it would be 40% probability. (A) N40 go trial that is accurately performed (correct button press under 400 ms). Feedback is 'hit', but because this is a neutral trial, no monetary reward is won. (B) R40 go trial that is accurately performed (correct button press under 400 ms). Feedback is 'hit', and because this is a reward trial, a 20¢ reward is won

2.4 | fMRI analysis

Only the stop trials were analysed, across all conditions and for both failed and successful inhibitions. This gave eight regressors of interest in our first-level GLM (four conditions for failed and successful inhibitions). These were all analysed for four different epochs:

(1) cue epoch, (2) anticipation epoch, (3) trial epoch (from onset of stop signal) and (4) feedback epoch. We modelled cue and anticipation epochs separately to investigate any possible brain activity differences during encoding of the cues, which are only presented during the cue epoch and not during the anticipation epoch. All task epochs apart from the epoch of interest was modelled as a regressor

FIGURE 2 Example sequences of stop trials. If the cue symbol was a dash ('-'), the upcoming trial was a neutral trial and no money could be won, irrespective of performance. If it was a dollar symbol ('$'), the upcoming trial would be a reward trial where monetary rewards could be won, depending on performance. If the colour of the symbol was white, there was a 20% probability that the upcoming trial would be a stop trial. If this colour was red, it would be 40% probability. (A) R20 stop trial with the stop signal appearing after 150-ms latency. In this example, the participant failed to inhibit a response and did not respond within the 400 ms. Feedback 'wrong' is given for responding (failed inhibition), and no reward is given as the response was not under 400 ms. (B) N20 stop trial with the stop signal appearing after 150-ms latency. In this example, the participant accurately inhibited their response (successful inhibition)
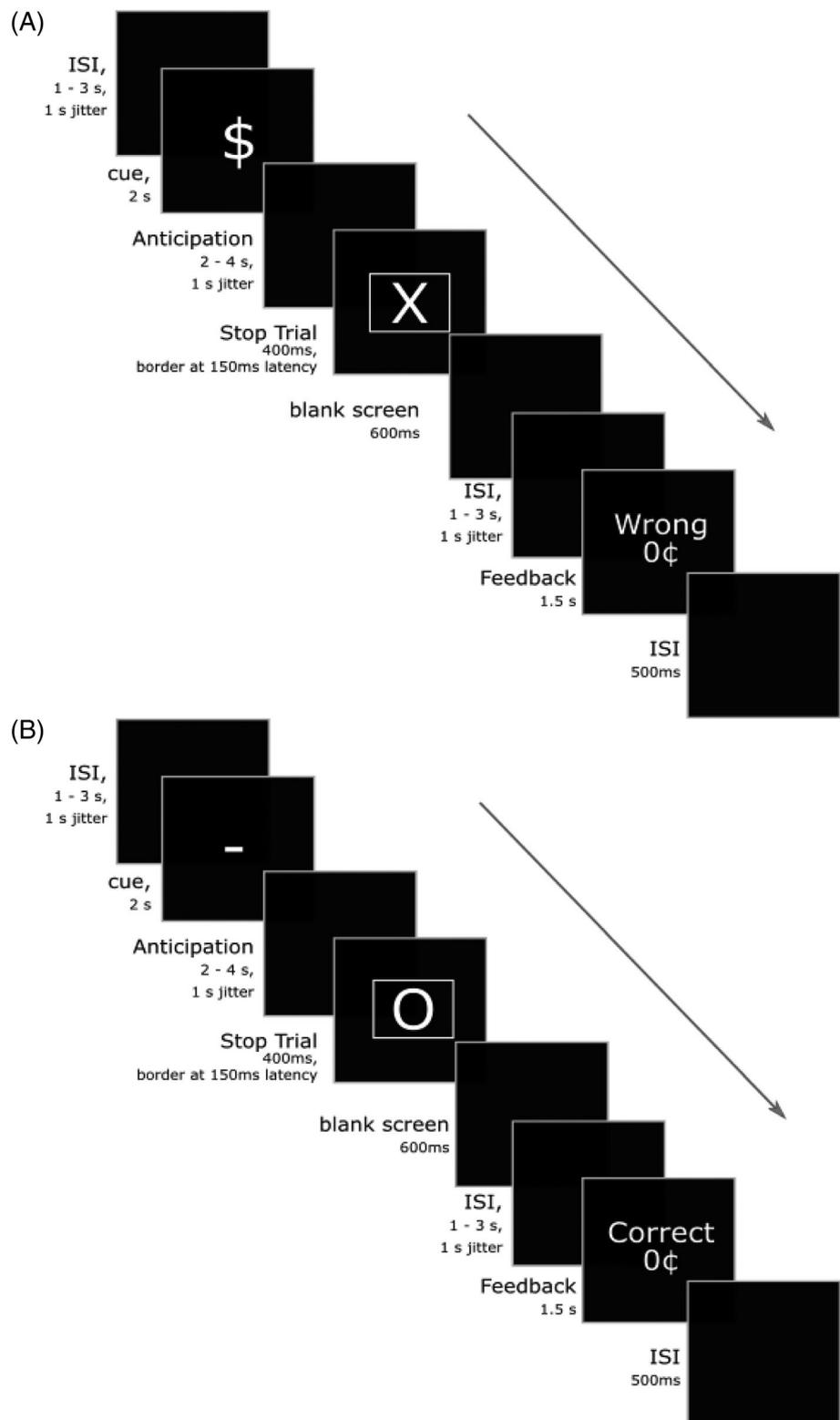
of no interest. For example, when analysing for effects at the stop trials for the cue epoch—all other epochs at these stop trials were modelled as regressors of no interest, in addition to also all epochs in go trials. This was done to reduce noise at our epoch and trial of interest, while reducing possible confounds from other trials and epochs. Lastly, for the feedback epoch, failed inhibitions where a

20¢ reward was won, was excluded. This was to remove any potential confound of the small 20¢ reward and to directly compare feedback of (1) 'correct 0c' for successful inhibitions and 'miss 0c' for failed inhibitions.

Second-level models were performed using a full-factorial, 2 × 2 × 2 ANOVA design. This included three factors, with two levels

each: (1) group (control and pTUD), (2) inhibition accuracy (failed and successful) and (3) reward (neutral trial or reward trial). Main effects and interactions were tested and, t-contrasts were done to examine condition-specific results. For model-based results, SSRTs for each participant, across each condition, were aligned and used as covariates of interests at the second level. This GLM consisted of cells for each reward and probability condition, for each of the two groups. There was no inhibition accuracy factor in this GLM as SSRT is not estimated for failed inhibitions (where a response is made). All data presented have threshold of $p < 0.05$ family-wise error corrected (FWE) at the cluster level, unless specified otherwise. Background brain image used for figures is from SPM canonical, which is an average T1 from 305 individuals, in MNI-space. Please see the Supporting Information for further fMRI analysis details.

3 | RESULTS

3.1 | Behaviour

3.1.1 | pTUD have similar stop accuracy scores to controls

As in Figure 3A, there were no significant differences in stop accuracy scores between groups (main effect of group: $F(1,38) = 3.2$, $p = 0.08$,

$\eta_p^2 = 0.078$) and no main effect of reward ($F(1,38) = 2.3$, $p = 0.13$, $\eta_p^2 = 0.058$). There was a main effect of probability ($F(1,38) = 65.95$, $p < 0.0001$, $\eta_p^2 = 0.63$), with performance better in the 40% probability condition compared with the 20%. There was also a significant group × probability interaction ($F(1,38) = 4.70$, $p = 0.036$, $\eta_p^2 = 0.11$), which appeared to be driven by the differences between pTUD and control groups in the N20 condition (t test, $p = 0.007$). Twelve participants from the pTUD group won the larger later $20 reward and 13 participants from the control group. This was won by successfully inhibiting a response on 60% or more of the reward stop trials. Overall, the stop-accuracy scores suggest that both groups perform better when cued that the upcoming trial has a higher probability of being a stop trial, and this is irrespective of whether this is a reward or a neutral trial. See Figure S1 for accuracy scores and reaction times for go trials.

3.1.2 | pTUD have slower SSRTs compared with controls

Figure 3B shows SSRT estimates where pTUD had a slower SSRT compared with controls (main effect of group: $F(1,37) = 8.09$, $p < 0.01$, $\eta_p^2 = 0.18$). While pTUD had a similar stop-accuracy score, the slower SSRT suggest the pTUD group found inhibiting a response
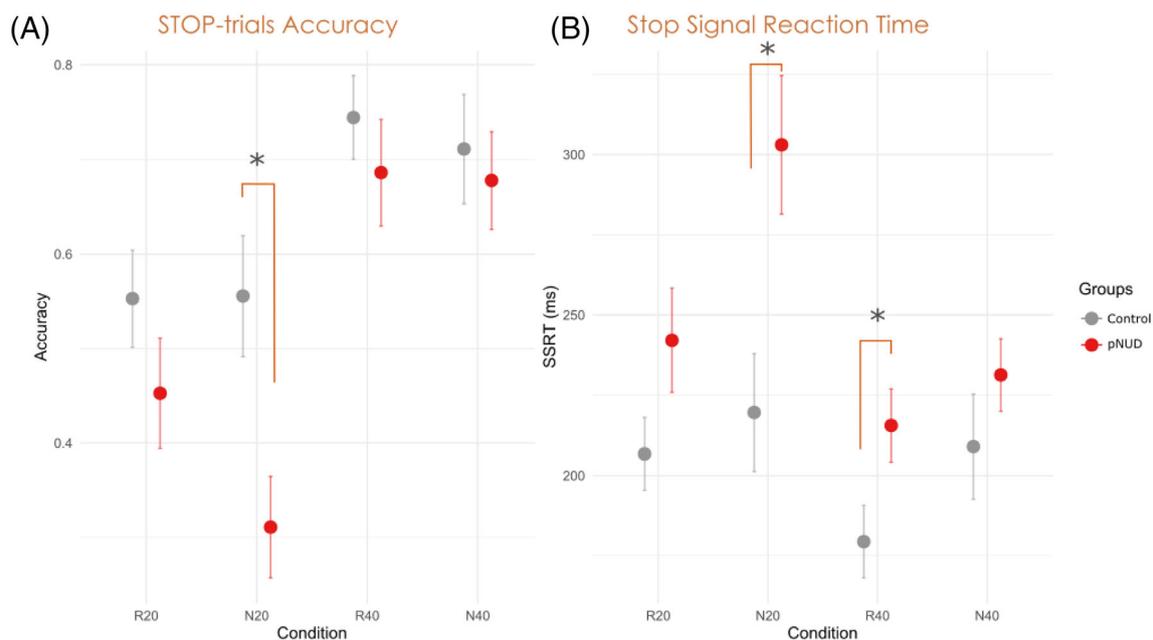
FIGURE 3 Inhibition accuracy measures for the people with a tobacco use disorder (pTUD) and control groups. (A) Stop trial accuracy scores. Both groups show similar performance here, with no main effect group $F(1,38) = 3.2$, $p = 0.08$, $\eta_p^2 = 0.078$. There is a main effect of probability $F(1,38) = 65.95$, $p < 0.0001^*$, $\eta_p^2 = 0.63$, and group × probability interaction $F(1,38) = 4.70$, $p = 0.036^*$, $\eta_p^2 = 0.11$. There was a significant difference between N20 condition for control and pTUD group (t test, $p < 0.01$). There were no significant main effect of reward ($F(1,38) = 2.3$, $p = 0.14$, $\eta_p^2 = 0.058$), no group and reward interaction ($F(1,38) = 1.3$, $p = 0.1$, $\eta_p^2 = 0.026$) and no three-way group, probability and reward interaction ($F(1,38) = 2.98$, $p = 0.09$, 0.073). (B) The pTUD group has slower SSRTs (main effect of group: $F(1,37) = 8.09$, $p < 0.01$, $\eta_p^2 = 0.18$). There is a significant main effect of reward ($F(1,37) = 12.96$, $p < 0.001$, $\eta_p^2 = 0.26$)* and probability ($F(1,37) = 13.13$, $p < 0.001$, $\eta_p^2 = 0.26$)*. There is a trend of a three-way interaction between group, probability and reward ($F(1,37) = 3.92$, $p = 0.055$, $\eta_p^2 = 0.096$). There were no significant two-way interactions between group and reward ($F(1,37) = 1.1$, $p = 0.3$, $\eta_p^2 = 0.03$), reward and probability ($F(1,37) = 0.8$, $p = 3.7$, $\eta_p^2 = 0.02$) and group and probability ($F(1,37) = 2.57$, $p = 0.12$, $\eta_p^2 = 0.065$). $^*p < 0.05$. pTUD, tobacco use disorder

more effortful than controls. Independent t tests indicated the pTUD group had a significantly slower SSRT for the N20 ($p = 0.0054$) and R40 ($p = 0.034$). There were no significant differences in the N40 ($p = 0.25$) and R20 ($p = 0.097$) conditions. We found a main effect of probability ($F(1,37) = 13.13$, $p < 0.001$, $\eta_p^2 = 0.26$) where the 40% condition had faster SSRTs. We also found a main effect of reward ($F(1,37) = 12.96$, $p < 0.001$, $\eta_p^2 = 0.26$) where reward trials had faster SSRTs. Lastly, there was no significant group and reward interaction ($F(1,37) = 1.1$, $p = 0.3$, $\eta_p^2 = 0.03$). Overall, we find that the pTUD group is more 'impulsive' in their responding based on their slower SSRTs.

3.2 | Brain fMRI activity

3.2.1 | Cue and anticipation epochs (preparatory control activity)

During the cue epoch, there is more activity in the striatum for reward trials, compared with neutral (Figure 4A). Failed inhibitions have greater precentral and posterior medial frontal cortex (pmFC) activity (Figure 4B). The pTUD group exhibits more control-related activity in the IFG, middle frontal gyrus (MFG) and superior frontal gyrus (SFG) compared with non-smokers, in reward trials that were successfully inhibited (Figure 4C). The pTUD group also has more activity in the precentral and postcentral gyri prior to successful inhibitions in the reward trials. Lastly, there was more activity in the fusiform gyrus for the 40% > 20% probability contrast (figure not shown), which is consistent with the literature on the fusiform gyrus' activation during the stop signal task, playing a role in correctly recognizing cues and their salience in inhibiting a response.[32-34]

There is greater striatal and insula activity at the anticipation epoch for reward > neutral trials (Figure 5A). Figure 5B shows activity in angular gyrus prior to successful inhibitions, consistent with previous literature.[8] Failed inhibitions (Figure 5C) have more activity in the precentral and postcentral gyri. There is also more activity in the medial cortical regions (anterior cingulate cortex [ACC], midcingulate cortex [MCC] and pmFC) associated with these failed inhibitions. The pTUD group in the anticipation epoch exhibits more control-related activity in the IFG and MFG, as well as precentral and postcentral activity (Figure 5D). Interestingly, pTUD in this epoch have more IFG activity even prior to failed inhibitions in the neutral trials (Figure 5E). See Tables S1 and S2 for a full list of brain regions activated in these epochs and their respective MNI coordinates and the second-level task activation in each group individually.
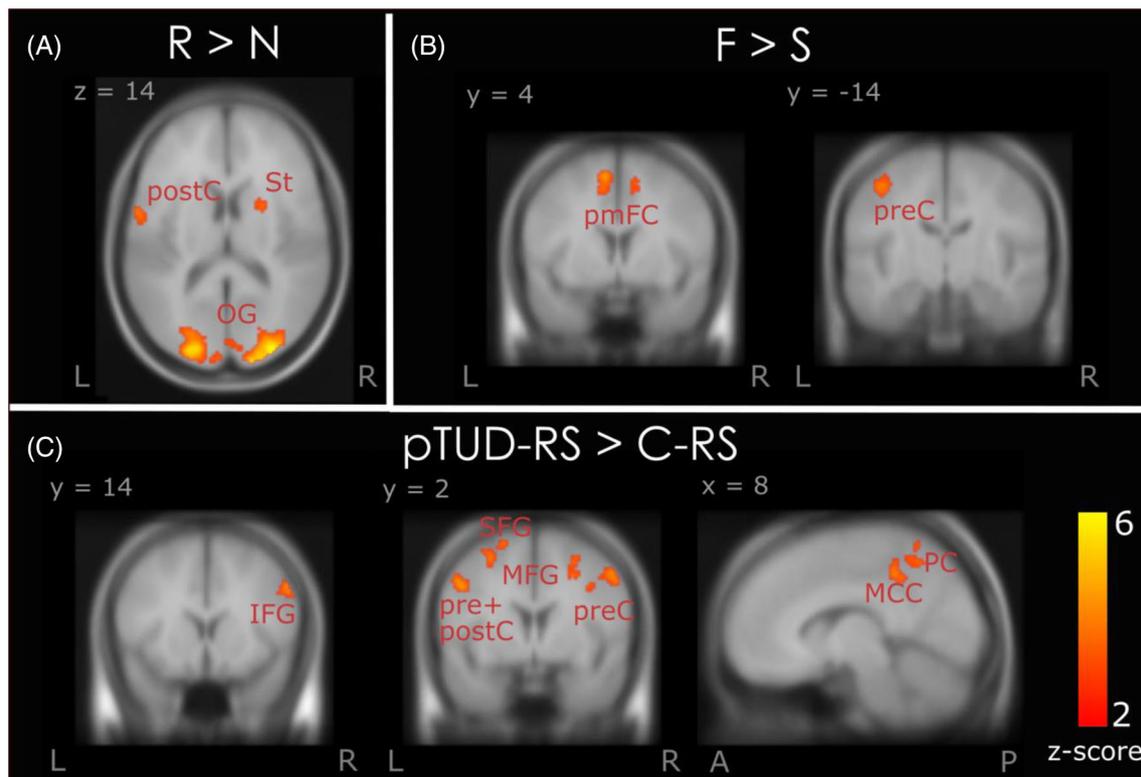
FIGURE 4 Activity during cue epoch. This is activity when participants are cued on the probability of an upcoming stop trial and whether it is a reward or a neutral trial. R, reward; N, neutral; F, failed inhibition; S, successful inhibition; pTUD, people with a tobacco disorder group; C, control group; PC, precuneus; St, striatum; pmFC, posterior medial frontal cortex; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; preC, precentral; postC, postcentral; MCC, midcingulate cortex; OG, occipital gyrus; L, left; R, right; A, anterior; P, posterior. *MFG + SFG activity in Figure 3C is pFWE = 0.055 (cluster level)
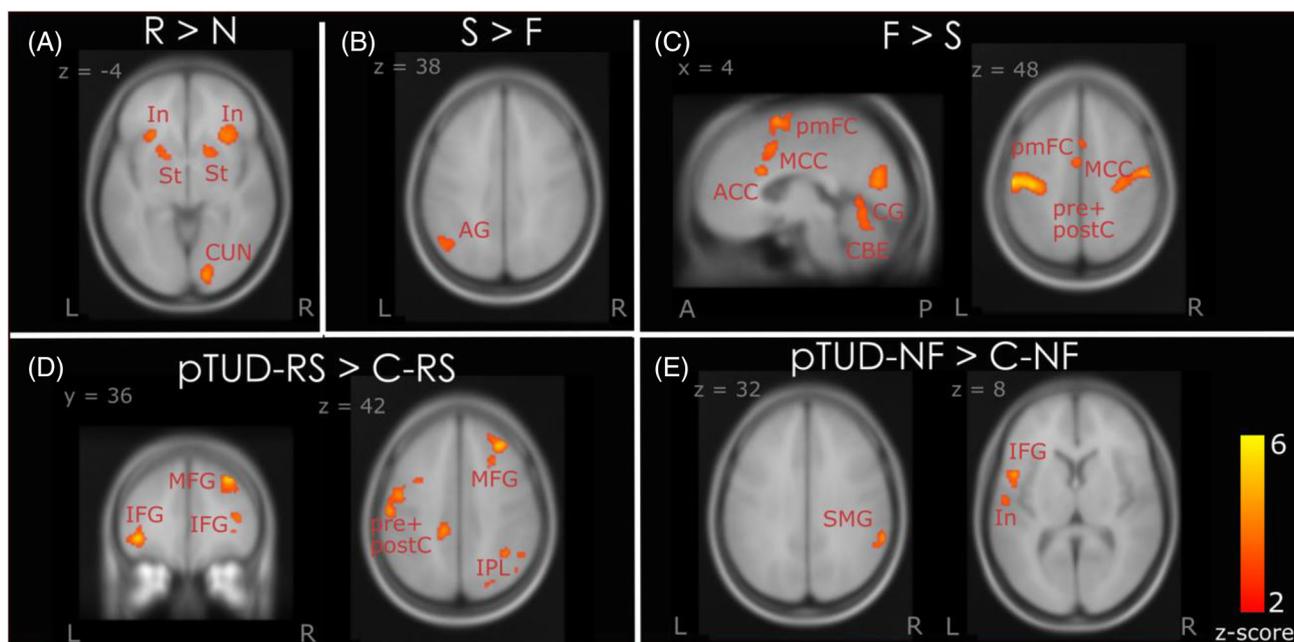
FIGURE 5 Brain activity during the anticipation epoch. This is activity immediately prior to the onset of the trial. R, reward; N. neutral; F, failed inhibition; S, successful inhibition; pTUD, people with a tobacco disorder group; C, control group; RS, reward successful inhibition trials; NF, neutral failed inhibition trials; In, insula; St, striatum; CUN, cuneus; ACC, anterior cingulate cortex; MCC, midcingulate cortex; pmFC, posterior medial frontal cortex; preC, precentral; postC, postcentral; IFG, inferior frontal cortex; SMG, supramarginal gyrus; MFG, middle frontal cortex; IPL, inferior parietal lobule; CBE, cerebellum; L, left; R, right; A, anterior; P, posterior; AG, angular gyrus
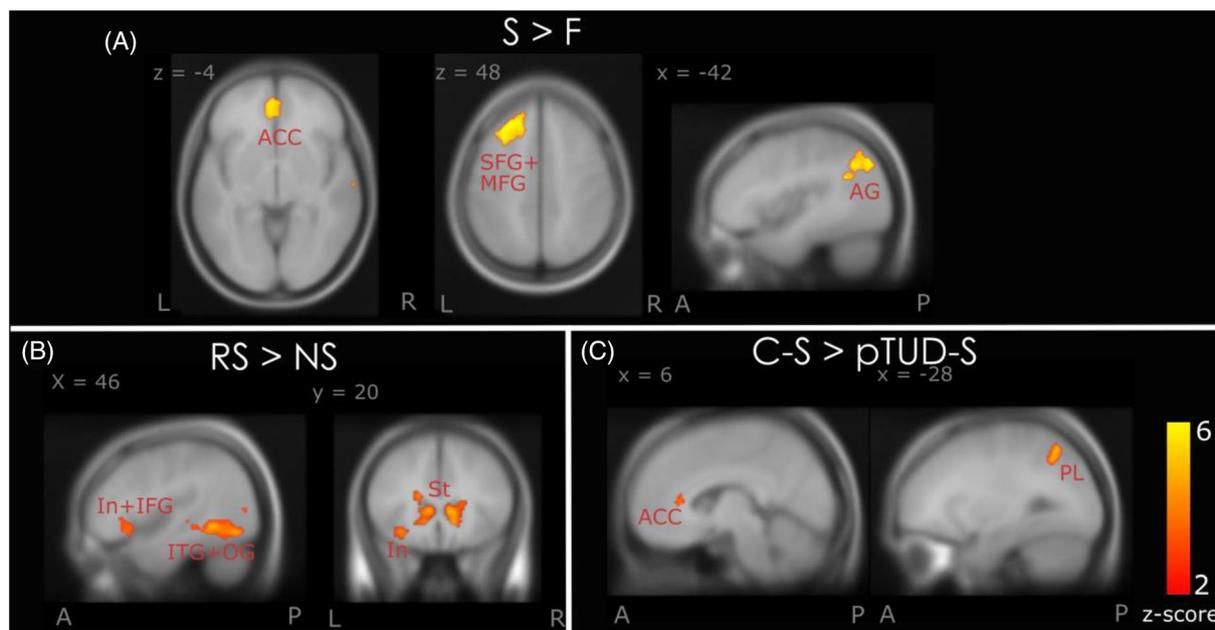
FIGURE 6 Brain activity at the stop-trial epoch. This is activity at the trial—when the stop signal is presented, and participants need to inhibit a response to make progress towards the larger later reward. R, reward; N, neutral; F, failed inhibition; S, successful inhibition; RS, reward successful inhibition trials; NS, neutral successful inhibition trials; pTUD, people with a tobacco disorder group; C, control group; ACC, anterior cingulate cortex; SFG, superior frontal gyrus; MFG, middle frontal gyrus; In, insula; IFG, inferior frontal gyrus; St, striatum; AG, angular gyrus; PL, parietal lobule; L, left; R, right; A, anterior; P, posterior. *The successful > failed inhibitions contrast here used threshold of $p < 0.05$ FWE corrected at whole brain level

3.2.2 | Stop trial epoch (reactive control activity)

Figure 6A shows the components of reactive control, where participants inhibit the prepotent response after seeing the stop signal. These successful inhibitions were associated with greater activity in control-related regions (ACC, SFG and MFG), as well as the angular gyrus (Figure 6A). Successfully inhibiting reward trials engages more IFG, insula and striatum compared with successfully inhibiting neutral trials (Figure 6B). Non-smokers have greater ACC activation compared with smokers (Figure 6C), and this may suggest that non-smokers have more reactive control. See Table S3 for a full list of brain regions activated in this epoch and their respective MNI coordinates and the second-level task activation in each group individually.

3.2.3 | Feedback epoch

Brain activity when processing feedback of 'correct 0c' after successful inhibitions, contrasted with 'miss 0c' after an incorrect response is shown in Figure 7A. Interestingly, there is striatal activity after

successful inhibitions. Following successful inhibitions, there was also more activity in the ACC, SFG and MFG. In contrast, there was more insula and pmFC activity following failed inhibitions (Figure 7B). The pTUD group exhibited greater pmFC and SFG activity following failed inhibitions in neutral trials compared with controls (Figure 7C). In contrast, after successful inhibitions for reward trials, the pTUD group had greater activity in the medial cortical regions (cingulate gyrus, SFG and pmFC) and the IFG. See Table S4 for a full list of brain regions activated in this epoch and their respective MNI coordinates and the second-level task activation in each group individually.

3.2.4 | Model-based SSRT brain activity correlations

The SSRT estimates of each participant across all conditions, between both groups, were used as covariates at the second-level analysis (Figure 8). Across all epochs, we found that with slower SSRTs in the pTUD group, there is more activity within the PFC and parietal regions.

FIGURE 7 Brain activity at the feedback epoch. This is activity at the feedback epoch, where participants are given feedback of 'correct 0c' for successful inhibitions and 'incorrect 0c' for failed inhibitions, where the response was slower than 400 ms or was the incorrect button press. R, reward; N, neutral; F, failed inhibition; S, successful inhibition; RS, reward successful inhibition trials; NS, neutral successful inhibition trials; pTUD, people with a tobacco disorder group; C, control group; ACC, anterior cingulate cortex; SFG, superior frontal gyrus; MFG, middle frontal gyrus; In, insula; IFG, inferior frontal gyrus; MCC, midcingulate gyrus; PCC, posterior cingulate cortex; pmFC, posterior medial frontal cortex; OG, occipital gyrus; St, striatum; Thal, thalamus; CBE, cerebellum; SMG, superior medial gyrus; AG, angular gyrus; L, left; R, right; A, anterior; P, posterior
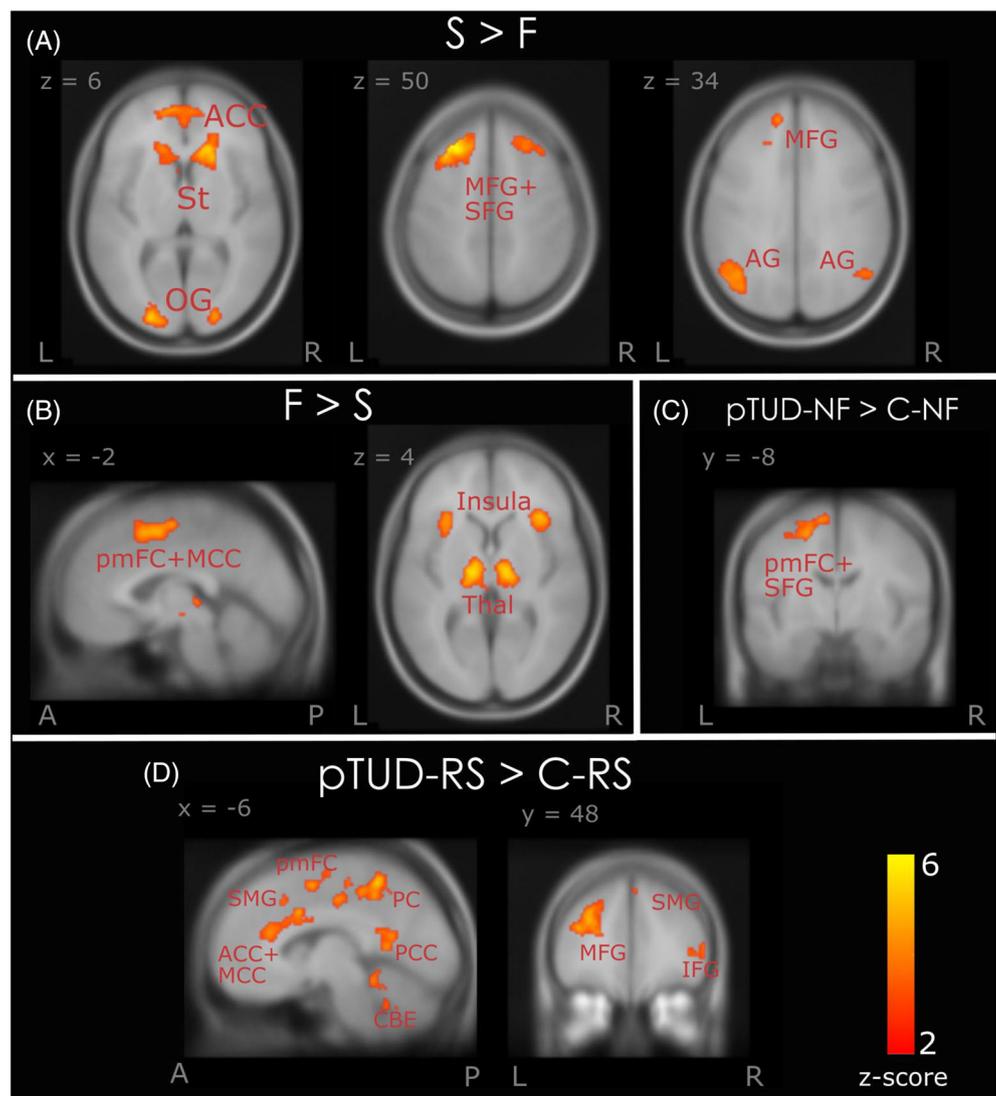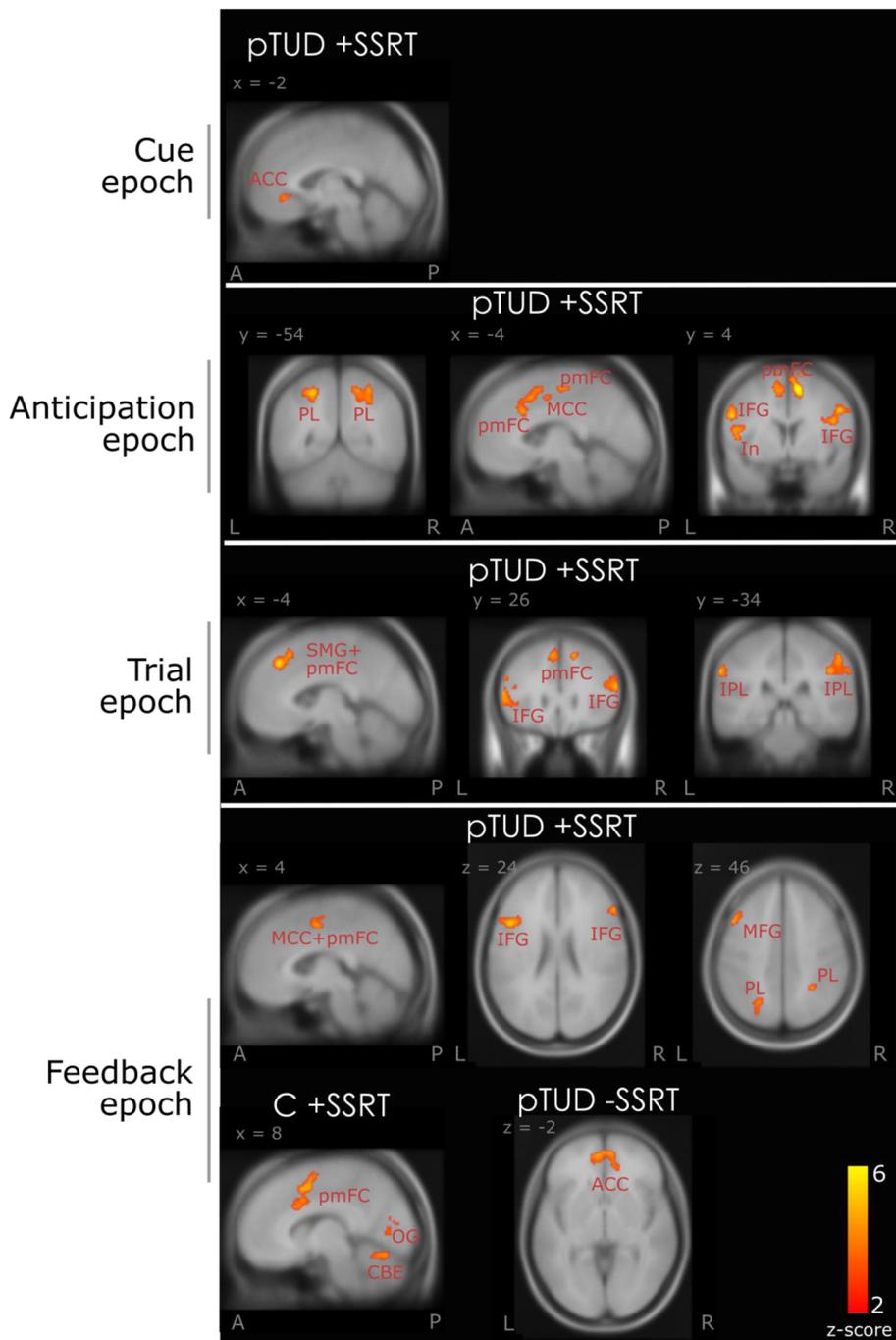
FIGURE 8 Brain activity correlating with SSRTs. pTUD+ SSRT, slower (increasing) SSRT correlating with the people with a tobacco disorder group; D− SSRT, faster (decreasing) SSRT correlating with the pTUD group; C+ SSRT, slower (increasing) SSRT correlating with the control group; ACC, anterior cingulate cortex; MCC, midcingulate cortex; pmFC, posterior medial frontal cortex; IFG, inferior frontal gyrus; SFG, superior frontal gyrus; MFG, middle frontal gyrus; IPL, inferior parietal lobe; PL, parietal lobule; CBE, cerebellum; OG, occipital gyrus

For the control group, we did not see SSRT brain correlations except for in the feedback epoch where a slower SSRT correlates with greater activity in the pmFC. See Table S5 for a full list of brain regions activated in this epoch and their respective MNI coordinates.

4 | DISCUSSION

Here, we investigated the underlying brain processes involved in exerting control over rewards in pTUD and healthy controls.

Overall, we found that pTUD do not differ from controls in their stop-accuracy scores (Figure 3A). However, they had slower SSRTs (Figure 3B). The combination of these findings suggests that pTUD require more effort and/or have a greater difficulty inhibiting their prepotent 'go processes'. This is consistent with previous findings where slower SSRTs were found in pSUD, including to nicotine[11,12] and a slower SSRT predicts a higher dependence to nicotine.[35] There was also a significant difference in the stop-accuracy score between groups specifically in the N20 condition, where the pTUD group had lower stop-accuracy scores. The difference here may

be due to the task design where neutral and reward conditions are interleaved. Another speculative possibility is that the pTUD group may prioritize their limited cognitive resources on inhibiting in other conditions,[36] because these other conditions may either lead to a reward (for R20 and R40 conditions) or have a higher chance of being a stop trial (N40 condition). Overall, the pTUD group's response inhibition performance was comparable with controls, but achieving parity required more cognitive effort.

The pTUD group did have greater activity in their cognitive control-related prefrontal regions (IFG and MFG) prior to successful inhibitions for reward trials. This was during both the cue and anticipation epochs. The increased activity might suggest the pTUD group engages in more preparatory control than healthy controls to achieve similar stop accuracies. Indeed, greater preparatory activity in prefrontal regions has previously been shown to aid in inhibitory processes.[7,8] Further, increased IFG activation for more difficult stops were previously reported.[37] The hypothesis that increased IFG activity in pTUD indicates more effort in stopping is consistent with our SSRT results. This finding of increased preparatory control in the pTUD group is contrary to another recent finding, in people with a cocaine use disorder, found to have reduced PFC related preparatory contol.[22] One explanation for the contrasting results may be due to the differences in the severity of dependence, where our sample had close to moderate levels and therefore may have a greater inhibitory control capacity relative to people with a cocaine use disorder. A second possibility is our short 3-h abstinence window, which may still produce some stimulant-related effects of nicotine and possibly cotinine (a metabolite of nicotine with a much longer half-life[38]) on cognition and may therefore facilitate this 'adaptive' pattern of behaviour where reduced reactive control is compensated for by increased preparatory control. Interestingly, the pTUD group also exhibits greater activity in the precentral and postcentral gyri, prior to successful inhibitions in reward trials. The increased precentral motor-related activity may be inhibited by the increased prefrontal control activity, contributing to the successful stop. Another possibility is that the precentral activation may be playing a role in motor inhibition as supported by findings from Li et al.,[39] where precentral activation correlated with smaller SSRTs (or efficient inhibitions).

The pTUD in the anticipation epoch had more IFG activity prior to failed inhibitions in neutral trials (Figure 5E). Increased IFG activity prior to failed inhibitions observed here suggests that greater preparatory IFG activity does not guarantee a successful inhibition and may also need engagement from other control-related prefrontal regions, such as MFG, as is the case prior to the successful inhibitions (Figure 5D). The finding that IFG may not guarantee a successful inhibition supports previous studies that find that IFG may play a non-specific role in response inhibition, for example, encoding other aspects of the task, such as attention, uncertainty and salience detection.[40] Overall, the pTUD group engages more preparatory control activity prior to successful inhibitions in reward trials, aiding them in achieving similar stop accuracy scores to the controls, albeit with slower SSRTs.

During the trial epoch, when the stop signal is detected, we see components of reactive control over reward. Successful inhibitions, across both groups, engaged more prefrontal control regions (MFG and SFG) and the ACC. These regions may aid in successfully inhibiting the go processes and therefore contribute to the successful stop. The ACC has been suggested to play a more complicated and non-specific role in the stop signal task[39]; however, one of its key roles has been implicated in inhibiting responses.[41] We therefore interpret ACC activity here as playing a role in facilitating response inhibition. Interestingly, the control group had greater ACC activity compared with the pTUD group during successful inhibitions in reward trials, suggesting that while the pTUD group may have an increased preparatory control, the control group has greater reactive control. The combination of these findings suggests that greater preparatory control (with increased IFG and MFG activity) reduces the need for high levels of reactive control to inhibit a prepotent response, as is the case for the dependent group. The control group, on the other hand, show less preparatory control but increased reactive control (with increased ACC activity) and can still reliably inhibit their responses. The control group may therefore find it less difficult to inhibit their responses and may not require the upregulated preparatory control for a successful stop. Our SSRT results showing the control group has shorter SSRTs is consistent with this interpretation in that they may find it less difficult to inhibit responses and therefore may rely less on increased preparatory control due to their higher levels of reactive control. Overall, both groups have similar inhibition accuracy but achieve this through different processes.

At the feedback epoch, there was increased striatal activation following successful inhibitions when contrasted with failed inhibitions, in both groups. Given the striatum's role in reward processing,[15] striatal activity here is consistent with participants anticipating the larger $20 reward, and this may play a role in motivating further response inhibitions to obtain the larger later reward. Further, the feedback of 'correct 0c' contrasted with 'miss 0c' may also exhibit a component of intrinsic reward processing for correctly performing the task. Contrary to our hypothesis, we did not see striatal activity during impulsive responses (for the smaller 20¢ reward), as previous studies have found.[16] Instead, the striatum was engaged during successful inhibitions in reward trials over neutral (Figure 6B). This may be due to the participants' goal of attaining the larger later reward as compared with the smaller sooner, where progress towards the larger later reward engaged striatal anticipatory activity. Therefore, the small 20¢ 'reward' may be considered neutral or even punishing by the participants given the context of the trials and the overall goal of attaining the larger later reward.

Following successful inhibitions (in the feedback epoch), there was also more activity in the ACC, SFG and MFG. These brain regions have previously been implicated in processing feedback, including positive feedback.[42,43] Interestingly, the pTUD group had greater activity in the medial cortical regions and the IFG, following successful inhibitions in reward trials, compared with controls.

Feedback processing and associated activity in these medial cortical regions have previously been shown to increase task performance.[43] One interpretation may be that increased activation in these regions for the pTUD group aids in improving stop accuracy scores to match those of the control group. Decreases in inhibitory control may lead to different compensatory neural strategies by the pTUD group and increasing feedback processing during successful inhibitions may therefore be one such compensatory neural strategy.

The model-based SSRT brain correlations showed that the pTUD group has more cognitive control-related activity correlating with slow SSRTs, across all epochs. On the contrary, the control group shows more control-related SFG and precentral activity to correlate with fast SSRTs, although only at a relaxed statistical threshold (SFG; $p = 0.066$ FWE [cluster level] and precentral; $p = 0.057$ FWE [cluster level]). Overall, one may expect greater engagement of these control-related regions to faster SSRTs, hence enabling more efficient stopping, as found by Galván et al.,[44] where both smokers and non-smokers had greater activity in control-related regions that correlated with faster SSRT. However, Galván et al.[44] did not find SSRT differences between groups. Other studies correlating SSRT scores with fMRI data have found that faster SSRTs correlate more strongly with control-related regions (medial cortical regions, SFG) and motor regions such as the presupplementary motor area and precentral.[39,45,46] These were all investigated in healthy non-smoker participants. Consistent with these studies, we found more precentral and PFC activity for the control group. However, for the pTUD group, it appears that slower SSRT engages more control-related regions. One interpretation to bring together these SSRT results across groups may be that the SSRTs reflect the cognitive effort required for stopping or difficulty in inhibiting. For the control group, more effort is required for fast inhibitions, hence greater control-related SFG activity. In contrast, the pTUD group appears to find the slower SSRTs more effortful, consistent with greater control-related PFC activity.

In sum, we find that both control and pTUD participants exhibit similar stop accuracy scores. However, the brain processes exhibited to achieve this are different between the two groups. The pTUD group shows greater inhibitory control-related activity prior to successful inhibitions over reward, whereas the control group exhibits greater reactive control with greater ACC activity during the inhibition epoch. Collectively, our results shed light on some of the brain processes involved in successfully exhibiting control over immediate small rewards in favour of greater delayed gratification in non-smokers and pTUD.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

All authors contributed to this paper. L. P. E. C. collected the data and performed preliminary analysis. R. H. designed the experiment and wrote the paper. M. I. G. wrote the paper. S. K. analysed the data and wrote the paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Redish AD, Jensen S, Johnson A. A unified framework for addiction: vulnerabilities in the decision process. *Behav Brain Sci*. 2008;31(4): 415-437. doi:10.1017/S0140525X0800472X
2. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry*. 2016;3(8):760-773. doi:10.1016/S2215-0366(16)00104-8
3. Verdejo-Garcia A, Chong TTJ, Stout JC, Yücel M, London ED. Stages of dysfunctional decision-making in addiction. *Pharmacol Biochem Behav*. 2018;164:99-105. doi:10.1016/j.pbb.2017.02.003
4. Bickel WK, Yi R, Mueller ET, Jones BA, Christensen DR. The behavioral economics of drug dependence: towards the consilience of economics and behavioral neuroscience. *Curr Top Behav Neurosci*. 2010; 3:319-341. doi:10.1007/7854_2009_22
5. Logan GD, Cowan WB. On the ability to inhibit thought and action: a theory of an act of control. *Psychol Rev*. 1984;91(3):295-327. doi: 10.1037/0033-295X.91.3.295
6. Aron AR, Poldrack RA. Cortical and subcortical contributions to stop signal response inhibition: role of the subthalamic nucleus. *J Neurosci*. 2006;26(9):2424-2433. doi:10.1523/JNEUROSCI.4682-05.2006
7. Chikazoe J, Jimura K, Hirose S, Yamashita KI, Miyashita Y, Konishi S. Preparation to inhibit a response complements response inhibition during performance of a stop-signal task. *J Neurosci*. 2009;29(50): 15870-15877. doi:10.1523/JNEUROSCI.3645-09.2009
8. Hu S, Li CSR. Neural processes of preparatory control for stop signal inhibition. *Hum Brain Mapp*. 2012;33(12):2785-2796. doi:10.1002/hbm.21399
9. Boehler CN, Appelbaum LG, Krebs RM, Hopf JM, Woldorff MG. Pinning down response inhibition in the brain - Conjunction analyses of the stop-signal task. *Neuroimage*. 2010;52(4):1621-1632. doi: 10.1016/j.neuroimage.2010.04.276
10. Brevers D, Bechara A, Kilts CD, et al. Competing motivations: proactive response inhibition toward addiction-related stimuli in quitting-motivated individuals. *J Gambl Stud*. 2018;34(3):785-806. doi: 10.1007/s10899-017-9722-2
11. Smith JL, Mattick RP, Jamadar SD, Iredale JM. Deficits in behavioural inhibition in substance abuse and addiction: a meta-analysis. *Drug*

Alcohol Depend. 2014;145:1-33. doi:10.1016/j.drugalcdep.2014.08.009

12. Charles-Walsh K, Furlong L, Munro DG, Hester R. Inhibitory control dysfunction in nicotine dependence and the influence of short-term abstinence. *Drug Alcohol Depend.* 2014;143:81-86. doi:10.1016/j.drugalcdep.2014.07.008

13. Feil J, Sheppard D, Fitzgerald PB, Yücel M, Lubman DI, Bradshaw JL. Addiction, compulsive drug seeking, and the role of frontostriatal mechanisms in regulating inhibitory control. *Neurosci Biobehav Rev.* 2010;35(2):248-275. doi:10.1016/j.neubiorev.2010.03.001

14. Knutson B, Westdorp A, Kaiser E, Hommer D. FMRI visualization of brain activity during a monetary incentive delay task. *Neuroimage.* 2000;12(1):20-27. doi:10.1006/nimg.2000.0593

15. Delgado MR. Reward-related responses in the human striatum. *Ann N Y Acad Sci.* 2007;1104(1):70-88. doi:10.1196/annals.1390.002

16. Oldham S, Murawski C, Fornito A, Youssef G, Yücel M, Lorenzetti V. The anticipation and outcome phases of reward and loss processing: a neuroimaging meta-analysis of the monetary incentive delay task. *Hum Brain Mapp.* 2018;39(8):3398-3418. doi:10.1002/hbm.24184

17. Balodis IM, Potenza MN. Anticipatory reward processing in addicted populations: a focus on the monetary incentive delay task. *Biol Psychiatry.* 2015;77(5):434-444. doi:10.1016/j.biopsych.2014.08.020

18. Solomon RL. The opponent-process theory of acquired motivation: the costs of pleasure and the benefits of pain. *Am Psychol.* 1980;35(8):691-712. doi:10.1037/0003-066X.35.8.691

19. Bjork JM. The ups and downs of relating nondrug reward activation to substance use risk in adolescents. *Curr Add Rep.* 2020;7(3):421-429. doi:10.1007/s40429-020-00327-7

20. Sherman L, Steinberg L, Chein J. Connecting brain responsivity and real-world risk taking: strengths and limitations of current methodological approaches. *Dev Cogn Neurosci.* 2018;33:27-41. doi:10.1016/j.dcn.2017.05.007

21. Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev Neurosci.* 2011;12(11):652-669. doi:10.1038/nrn3119

22. Nigam KB, Straub LK, Zuniga EA, et al. Blunted prefrontal signature of proactive inhibitory control in cocaine use disorder. *Drug Alcohol Depend.* 2021;218:108402. doi:10.1016/j.drugalcdep.2020.108402

23. Chikara RK, Chang EC, Lu YC, Lin DS, Lin CT, Ko LW. Monetary reward and punishment to response inhibition modulate activation and synchronization within the inhibitory brain network. *Front Hum Neurosci.* 2018;12:27. doi:10.3389/fnhum.2018.00027

24. Boehler CN, Schevernels H, Hopf JM, Stoppel CM, Krebs RM. Reward prospect rapidly speeds up response inhibition via reactive control. *Cogn Affect Behav Neurosci.* 2014;14(2). doi:10.3758/s13415-014-0251-5, 593, 609

25. Padmala S, Pessoa L. Reward reduces conflict by enhancing attentional control and biasing visual cortical processing. *J Cogn Neurosci.* 2011;23(11):3419-3432. doi:10.1162/jocn_a_00011

26. Rosell-Negre P, Bustamante JC, Fuentes-Claramonte P, Costumero V, Llopis-Llacer JJ, Barrós-Loscertales A. Reward contingencies improve goal-directed behavior by enhancing posterior brain attentional regions and increasing corticostriatal connectivity in cocaine addicts. *PLoS One.* 2016;11(12):e0167400. doi:10.1371/journal.pone.0167400

27. Epping-Jordan MP, Watkins SS, Koob GF, Markou A. Dramatic decreases in brain reward function during nicotine withdrawal. *Nature.* 1998;393(6680):76-79. doi:10.1038/30001

28. Verbruggen F, Logan GD. Models of response inhibition in the stop-signal and stop-change paradigms. *Neurosci Biobehav Rev.* 2009;33(5):647-661. doi:10.1016/j.neubiorev.2008.08.014

29. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia.* 1971;9(1):97-113. doi:10.1016/0028-3932(71)90067-4

30. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict.* 1991;86(9), 1119-1127. doi:10.1111/j.1360-0443.1991.tb01879.x

31. Benowitz NL, Jacob P, Jones RT, Rosenberg J. Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. *J Pharmacol Exp Ther.* 1982;221(2):368-372.

32. Pawliczek CM, Derntl B, Kellermann T, Kohn N, Gur RC, Habel U. Inhibitory control and trait aggression: neural and behavioral insights using the emotional stop signal task. *Neuroimage.* 2013;79:264-274. doi:10.1016/j.neuroimage.2013.04.104

33. Fauth-Bühler M, de Rover M, Rubia K, et al. Brain networks subserving fixed versus performance-adjusted delay stop trials in a stop signal task. *Behav Brain Res.* 2012;235(1):89-97. doi:10.1016/j.bbr.2012.07.023

34. Simmonds DJ, Pekar JJ, Mostofsky SH. Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. *Neuropsychologia.* 2008;46(1):224-232. doi:10.1016/j.neuropsychologia.2007.07.015

35. Billieux J, Gay P, Rochat L, Khazaal Y, Zullino D, Van der Linden M. Lack of inhibitory control predicts cigarette smoking dependence: evidence from a non-deprived sample of light to moderate smokers. *Drug Alcohol Depend.* 2010;112(1–2):164-167. doi:10.1016/j.drugalcdep.2010.06.006

36. Cepeda-Benito A, Tiffany ST. The use of a dual-task procedure for the assessment of cognitive effort associated with cigarette craving. *Psychopharmacology (Berl).* 1996;127(1):155-163. doi:10.1007/bf02805989

37. Hughes ME, Johnston PJ, Fulham WR, Budd TW, Michie PT. Stop-signal task difficulty and the right inferior frontal gyrus. *Behav Brain Res.* 2013;256:205-213. doi:10.1016/j.bbr.2013.08.026

38. Grizzell JA, Echeverria V. New insights into the mechanisms of action of cotinine and its distinctive effects from nicotine. *Neurochem Res.* 2014;40(10):2032-2046. doi:10.1007/s11064-014-1359-2

39. Li CSR, Huang C, Constable RT, Sinha R. Imaging response inhibition in a stop-signal task: neural correlates independent of signal monitoring and post-response processing. *J Neurosci.* 2006;26(1):186-192. doi:10.1523/JNEUROSCI.3741-05.2006

40. Hampshire A, Chamberlain SR, Monti MM, Duncan J, Owen AM. The role of the right inferior frontal gyrus: inhibition and attentional control. *Neuroimage.* 2010;50(3):1313-1319. doi:10.1016/j.neuroimage.2009.12.109

41. Albert J, López-Martín S, Tapia M, Montoya D, Carretié L. The role of the anterior cingulate cortex in emotional response inhibition. *Hum Brain Mapp.* 2012;33(9):2147-2160. doi:10.1002/hbm.21347

42. Mies GW, van der Molen MW, Smits M, Hengeveld MW, Van der Veen FM. The anterior cingulate cortex responds differently to the validity and valence of feedback in a time-estimation task. *Neuroimage.* 2011;56(4):2321-2328. doi:10.1016/j.neuroimage.2011.04.015

43. Luft CDB. Learning from feedback: the neural mechanisms of feedback processing facilitating better performance. *Behav Brain Res.* 2014;261:356-368. doi:10.1016/j.bbr.2013.12.043

44. Galván A, Poldrack RA, Baker CM, McGlennen KM, London ED. Neural correlates of response inhibition and cigarette smoking in late adolescence. *Neuropsychopharmacology*. 2011;36(5):970-978. doi:10.1038/npp.2010.235

45. Chao HHA, Luo X, Chang JLK, Li CSR. Activation of the pre-supplementary motor area but not inferior prefrontal cortex in association with short stop signal reaction time—an intra-subject analysis. *BMC Neurosci*. 2009;10(1):1-10. doi:10.1186/1471-2202-10-75

46. Li CSR, Luo X, Yan P, Bergquist K, Sinha R. Altered impulse control in alcohol dependence: neural measures of stop signal performance. *Alcohol Clin Exp Res*. 2009;33(4):740-750. doi:10.1111/j.1530-0277.2008.00891.x

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