Published in final edited form as:

Neuropsychologia. 2015 February ; 68: 218–231. doi:10.1016/j.neuropsychologia.2015.01.016.

Suppressing a motivationally-triggered action tendency engages a response control mechanism that prevents future provocation

Scott M. Freeman, Dominic Alvernaz, Alexandra Tonnesen, David Linderman, and Adam R. Aron

Department of Psychology, University of California, San Diego, La Jolla, California, USA

Abstract

Reward-predicting stimuli can induce maladaptive behavior by provoking action tendencies that conflict with long-term goals. Earlier, we showed that when human participants were permitted to respond for a reward in the presence of a task-irrelevant, reward-predicting stimulus (i.e. goCS+ trials), the CS+ provoked an action tendency to respond compared to when a non-rewarding CS– stimulus was present (i.e. goCS– trials). However, when participants were not permitted to respond, response suppression was recruited to mitigate the action tendency that was triggered by the motivating CS+ stimulus (i.e. on nogoCS+ trials) (Freeman, Razhas, & Aron, 2014). Here we tested the hypothesis that repeated response suppression over a motivationally-triggered action tendency would reduce subsequent CS+ provocation. We compared groups of participants who had different proportions of nogoCS+ trials, and we measured CS+ provocation on go trials via reaction time. Our results showed that CS+ provocation on go trials was reduced monotonically as the proportion of nogoCS+ trials increased. Further analysis showed that these group differences were best explained by reduced provocation on goCS+ trials that followed nogoCS+ (compared to nogoCS–) trials. Follow-up experiments using a neurophysiological index of motor activity replicated these effects and also suggested that, following nogoCS+ trials, a response suppression mechanism was in place to help prevent subsequent CS+ provocation. Thus, our results show that performing response suppression in the face of a motivating stimulus not only controls responding at that time, but also prevents provocation in the near future.

Keywords

cognitive control; motivation; conflict adaptation; Pavlovian-to-instrumental transfer; Transcranial Magnetic Stimulation

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Correspondence should be addressed to: Dr. Adam R. Aron, Department of Psychology, University of California, San Diego, 92093, adamaron@ucsd.edu, Phone: 858.822.1096.

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1. INTRODUCTION

The environment is filled with reward-predicting, Pavlovian stimuli that can motivate our actions (Cavanagh, Eisenberg, Guitart-Masip, Huys, & Frank, 2013; Gupta & Aron, 2011; Hajcak et al., 2007; Talmi, Seymour, Dayan, & Dolan, 2008) and bias our decisions (Bray, Rangel, Shimojo, Balleine, & O'Doherty, 2008; Chiu, Cools, & Aron, 2014; Klein-Flügge & Bestmann, 2012). Such stimuli can be beneficial when obtaining the reward is congruent with our goals (e.g., a marathon runner running faster after passing a picture of a gold medal). Oftentimes, however, appetitive Pavlovian stimuli can motivate actions that conflict with our goals (e.g., a recovering smoker who buys cigarettes after smelling smoke), resulting in “misbehavior of the will” (Dayan, Niv, Seymour, & Daw, 2006). It is therefore essential that, in such circumstances, we learn to control action tendencies that are provoked by appetitive, motivating stimuli.

In an experimental setting, the way in which Pavlovian stimuli motivate our actions towards rewards can be studied by taking advantage of a phenomenon called Pavlovian-to-instrumental transfer (PIT). For a typical PIT task, the participant first undergoes a session of instrumental training and a session of Pavlovian training to develop response-reward and stimulus-reward relationships, respectively. Then, in the Transfer phase, the Pavlovian stimuli are incidentally presented while the participant again engages in instrumental, reward-driven behavior¹ (Corbit & Balleine, 2005; Holmes, Marchand, & Coutureau, 2010). A “PIT effect” occurs when, in the Transfer phase, Pavlovian stimuli previously paired with reward invigorate instrumental responding compared to stimuli not previously paired with reward.

In an earlier study, we used a novel hybrid go-nogo/PIT task to examine how control is implemented over a motivating stimulus that provokes action tendencies (Freeman et al., 2014). This task began with an Instrumental phase where thirsty participants were either permitted (go trials) or not permitted (nogo trials) to make instrumental presses for a juice reward. On go trials, participants made quick and repeated presses and received a drop of juice if enough presses were made based on a variable ratio reward schedule. On nogo trials, participants had to refrain from responding and no juice was delivered. If they mistakenly pressed on nogo trials, then a ‘Do Not Press’ signal was given. After this phase, participants underwent the Pavlovian phase, where they learned to associate a particular color with juice reward and another color with no juice reward (the CS+ and CS–, respectively). In the final phase (Transfer), instrumental responses were made with the motivating (CS+) or non-motivating (CS–) stimulus in the background.

Our main focus of analysis was the Transfer phase, where participants made instrumental responses (go trials) or refrained from responding (nogo trials) in the presence of a motivating (CS+) or a non-motivating (CS–) stimulus. On go trials, instrumental responding was invigorated in the presence of the CS+ compared to the CS– (i.e. the PIT effect). Specifically, we showed that people responded faster on their first press (first press reaction

¹The Transfer phase is generally done in extinction, where no rewards are delivered. However, in our adapted version of the PIT task, we continue to reward instrumental behavior in the Transfer phase in order to maximize motivational drive.

time, RT) and also made more presses for CS+ versus CS-. On nogo trials, there was an increased commission error rate when the CS+ was present. This failure to withhold a response when provoked suggests either that responses were too energized or that a mechanism of response suppression was not always effective in mitigating the action tendencies generated by the CS+.

2. Single-pulse transcranial magnetic stimulation

The behavioral results described above suggest that the CS+ quickly energizes a response, and that, in a nogo context, response activation has to be quickly overcome by a putative response suppression mechanism. To better visualize this activation/suppression process, we previously used single-pulse transcranial magnetic stimulation (spTMS) to probe the underlying motor physiology (see Freeman et al., 2014 for details). On each trial, a single pulse was delivered over the scalp corresponding to the right hand finger muscles. The pulse evoked a response that was recorded with concurrent electromyography (EMG)—the so-called motor evoked potential (MEP). The MEP is an index of corticospinal excitability, which reflects cortical, subcortical, and spinal influences. This method allows one to measure the amount of activation of a muscle representation in the brain even without overt action. When MEPs are reduced beneath a baseline, it is often interpreted as suppression of the response tendency (Cai, Oldenkamp, & Aron, 2011; Duque, Lew, Mazzocchio, Olivier, & Richard, 2010). We delivered spTMS in the Transfer phase 250 milliseconds (ms) after go and nogo cues (for CS+ and CS-). On go trials, MEPs were greater for CS+ compared to both CS- and baseline several hundred ms before a response was made, providing further evidence for quick provocation by the CS+. On correct nogo trials, mean MEPs were beneath baseline for CS+ (but not CS-) trials, which suggests that response suppression was triggered by the conflict between the motivationally-triggered activation and the nogo cue. These spTMS results support the hypothesis that response suppression can be recruited to control a motivationally-triggered action tendency.

3. The current study

It is of considerable theoretical and practical significance to develop behavioral methods to reduce and/or prevent the motivational provocation of stimuli. Here we tested the idea that, in the Transfer phase, repeated implementation of putative response suppression on nogoCS+ trials would lead to reduced provocation from the CS+ on go trials. This idea is suggested by recent studies using Go/NoGo-like paradigms, in which withholding responding (“nogo-ing”) to reward-related stimuli leads to an apparent decrease in the hedonic value of those stimuli when compared to “going” (Fenske, Raymond, Kessler, Westoby, & Tipper, 2005; Ferrey, Frischen, & Fenske, 2012; Houben & Jansen, 2011; Kiss, Raymond, Westoby, Nobre, & Eimer, 2008; Wessel, Doherty, Berkebile, Linderman, & Aron, in press). These results have been interpreted as an “inhibitory devaluation”, whereby response suppression during nogo trials leads to a reduction in the “value” or “motivational incentive” of reward-related stimuli (Frischen, Ferrey, Burt, Pistchik, & Fenske, 2012).

In Experiment 1, we tested the hypothesis that response suppression over a motivationally-triggered action tendency would reduce quick provocation from a motivating stimulus by

manipulating the number of times that this mechanism was recruited. Specifically, we varied the proportions of nogoCS+ and nogoCS– trials in three independent groups of participants, while holding the proportions of goCS+ and goCS– trials constant. This allowed us to examine if increasing the number of nogoCS+ trials would affect the quick motor energization (reflected in first press RTs) of the CS+ on go trials. Our hypothesis was that, in the group with the highest proportion of nogoCS+ trials, having to perform response suppression more often would lead to a change in the motivating properties of the CS+, which could be examined by comparing RTs for CS+ and CS– on go trials (i.e. the PIT effect). Specifically, we predicted a decreased PIT effect as a function of a greater proportion of nogoCS+ trials. To presage the results, we show that this was the case, as the group PIT effect decreased monotonically with an increasing proportion of nogoCS+ trials. Upon further analysis, it appeared that the best explanation of this result was that nogoCS+ trials reduced provocation if a CS+ (but not a CS–) occurred on the next trial. In three follow-on experiments, we aimed to replicate and further explore these results. We examined trial-by-trial effects, whereby goCS+ followed nogoCS+ or nogoCS– trials. We used spTMS to test when in time, and how, the response suppression on nogoCS+ putatively affects the next trial.

4. EXPERIMENT 1

4.1. METHOD

4.1.1. Participants—Sixty-two undergraduates (twenty males) from the University of California, San Diego participated for course credit (mean age = 20.51, SD = 1.79). All reported normal or corrected-to-normal visual acuity and provided written informed consent according to a local institutional review board protocol. Data from one participant was excluded due to a failure to properly understand the task and data from another participant was excluded due to a technical malfunction with the juice pump.

4.1.2. Stimuli and procedure—Participants were instructed to abstain from all liquids for a minimum of three hours before arriving at the lab. Upon arrival, each participant completed a pre-experiment questionnaire that surveyed 1) the number of hours since the last consumption of liquid, 2) the type of juice that the participant preferred to consume throughout the experiment (there were four possible juice types: peach Snapple, apple juice, orange juice, and fruit punch), 3) the participant's thirst level (1–7 Likert scale; 1 – Not at all, 7 – Extremely), 4) how much the participant liked the juice that he or she selected (1–7 Likert scale; 1 – Very little, 7 – Very much), and 5) how much the participant wanted the juice at that moment (1–7 Likert scale; 1 – Not at all, 7 – A lot). To proceed with the experiment, a rating of 5 or higher was required for the “wanting of juice” item. If the initial rating was below a 5, the participant (after consenting) consumed salty pretzels to increase thirst level. Then, the participant re-rated his or her thirst level and how much he or she wanted the juice to verify it was at least a 5, which was the case in all participants.

After the participant selected a juice, the experimenter filled a syringe with approximately 65 mL of the selected juice and securely placed the syringe in the juice pump. Juice was delivered by a NE-500 OEM syringe pump (New Era Pump Systems, Inc., NY). Connected to the pump was a ~1.5 meter long polyethylene plastic tube, followed by a connector piece

and approximately 3 more inches of tubing that was newly replaced for each participant. The 3-inch tubing was cleaned in front of the participant via a rubbing alcohol pad before the experiment began. Each participant sat in front of an iMac (Apple Inc., Cupertino, CA) with a 20-inch monitor (60 Hz refresh rate) and made responses on a button pad that was placed approximately 12-inches from the monitor. Throughout the experiment, approximately one inch of tubing rested comfortably in the mouth of the participant (Figure 1B). Juice delivery was triggered via customized Matlab scripts.

Following the Pavlovian phase (just before the Transfer phase), participants completed a questionnaire that again inquired about their thirst level, as well as their “liking” and “wanting” of the juice. Analyzing such variables before the Transfer phase allowed us to determine if there were any group differences in motivation for juice after participants consumed juice during the Instrumental and Pavlovian phases. Finally, we repeated this questionnaire after the Transfer phase to determine if any group differences emerged towards the end of the experiment.

4.1.3. Task design—The experiment consisted of three main phases: Instrumental, Pavlovian, and Transfer. In the Instrumental phase, participants were presented with a large gray rectangle on a black background. In the center of the screen, there was a black triangle or a black square for 2.5 seconds (s) (Figure 1A). For each participant, one shape was randomly selected as the go cue and the other the nogo cue. Upon presentation of the go cue, the participant could continuously press a button with his or her right index finger to obtain a drop of juice (0.5 milliliters). Juice was delivered on a variable ratio reward schedule (5–15 presses; 10 on average) and the number of presses required on a given trial was randomly generated and pre-determined (i.e. assigned before the experiment began) for each participant. Information regarding the number of presses required for juice delivery was not disclosed to the participants, though they were informed that the required number of presses would vary across trials. If the button was pressed enough times for juice delivery on a given trial, a small black circle appeared above the square to signify imminent juice delivery, which always came at the end of the 2.5 s trial. This circle allowed participants to gain a general understanding of how many presses were needed for juice delivery. Upon presentation of a nogo cue, participants were required to withhold responding. If a press was made on a nogo trial, a red error message reading, “Do Not Press the Button!” was flashed for 1 s. All trials were separated by a fixation cross for a variable inter-trial-interval (ITI) of 3–5 s and were presented pseudo-randomly such that no more than three go or nogo cues could occur in succession. There were 24 total trials (12 per condition), and all participants engaged in a practice instrumental session of 12 trials (6 per condition).

In the Pavlovian phase, a large purple or green rectangle appeared on either the left or right side of the computer screen with a black background (Figure 1A). If the rectangle appeared on the left or right side of the screen, participants pressed with the middle or index finger of their left hand, respectively, as fast as possible. One color was always associated with juice delivery (CS+), while the other color was always associated with no juice delivery (CS–). The CS+ and CS– colors were randomized across participants. For CS+ trials, juice was always delivered 1.5 s after stimulus onset and the rectangle remained on the screen for an additional 1.5 s for a total trial duration of 3 s. Participants were instructed that juice

delivery was in no way contingent on their responding, both in terms of the finger pressed and speed of the press. They were also instructed that juice delivery would be related to the color of the rectangle, though neither the color, nor the strength of the contingency was revealed. All trials were presented pseudo-randomly with a variable 3–5 s ITI that included a white fixation cross placed at the center of the screen. There were 60 total trials (15 CS+ right side, 15 CS+ left side, 15 CS– right side, 15 CS– left side).

The Transfer phase was identical to the Instrumental phase, with several exceptions. First, there was no longer a black circle to indicate impending juice delivery. This encouraged participants to keep pressing throughout the trial because they did not know if juice would be delivered. Second, the Transfer phase had three blocks, each consisting of 40 trials (120 total trials). Third, the background color (which appeared at the same time as the go/nogo cue) was green or purple (CS+ or CS–) rather than gray, yielding four trial types: 1) goCS+, 2) goCS–, 3) nogoCS+, and 4) nogoCS–. For all participants, goCS+ trials and goCS– trials each comprised 25% of Transfer trials. Importantly, however, the proportion of nogoCS+ and nogoCS– trials varied across participants, who were placed in one of three experimental groups: 1) 40% nogoCS+, 10% nogoCS– (High Group); 2) 25% nogoCS+, 25% nogoCS– (Equal Group); and 3) 10% nogoCS+, 40% nogoCS– (Low Group) (Figure 1B). The computer randomly assigned each participant to one of the three groups. This assignment was blind to both the participants and the experimenter. There were 20 participants in each group.

4.1.4. Data Analysis—We first verified that conditioning took place and did not differ across groups by examining mean RTs for CS+ and CS– trials during the Pavlovian phase. RTs values were entered into a mixed-model ANOVA with Stimulus (CS+/CS–) as a within-subject factor and Group (High/Equal/Low) as a between-subject factor. We then tested for conditioning effects (CS+ versus CS–) in each group separately using paired t-tests.

Our primary dependent measure was first press RT on go trials during the Transfer phase, which provided an index of quick motor provocation generated by the motivating (CS+) stimulus compared to the non-motivating (CS–) stimulus (i.e. the PIT effect). For each participant, we calculated mean first press RTs for goCS+ and goCS– trials, collapsed across the three Transfer blocks. We then took the difference score of the two trial types (goCS+ minus goCS–) to provide a measure of the PIT effect. We treated Group as a categorical variable (Low/Equal/High) and tested for group differences in the PIT effect.

As the RT values were non-normally distributed (Shapiro-Wilk test: $W = 0.92$, $p = 0.001$), we used a non-parametric Kruskal-Wallis test to examine group differences in the PIT effect. This was followed by post-hoc comparisons using two-tailed Wilcoxon rank-sum tests. To assess PIT effects for each group separately, the group PIT effect was compared to a value of 0 (representing no difference between goCS+ and goCS–) using two-tailed Wilcoxon signed rank tests. Trials were excluded if RTs were less than 150 ms or no response was given.

4.2. RESULTS

4.2.1. Pavlovian conditioning—ANOVA showed a significant main effect of Stimulus ($F_{1,57} = 63.18$, $p < 0.001$), with faster RTs for CS+ (473.6 ms) compared to CS- (527.1 ms). Paired t-tests showed that all three groups exhibited a significant conditioning effect (all P s < 0.001), with faster RTs for CS+ compared to CS-. Importantly, the Stimulus $\times$ Group interaction was not significant ($F_{2,57} = 2.11$, $p = 0.13$), indicating no significant group differences in the amount of conditioning that took place during the Pavlovian phase (Low: $M = 42.6$ ms, $SD = 42.9$ ms; Equal: $M = 44.8$ ms, $SD = 36.4$ ms; High: $M = 73$ ms, $SD = 70.6$ ms). Paired-tests further confirmed no significant differences in conditioning between any of the groups (all P s > 0.05), though the High group showed a trend towards larger conditioning effects than the Low ($p = 0.071$) and Equal ($p = 0.092$) groups. Notably, greater CS+ vs. CS- conditioning in the High group would, if anything, bias against our prediction of a reduced PIT effect for the High group.

4.2.2. PIT effects in Transfer phase—Our primary analysis of Group (High/Equal/Low) with the PIT effect (goCS+ minus goCS- for first press RT) as the dependent measure revealed a significant difference between groups, $\chi^2(2) = 11.3$, $p = 0.003$, in which higher proportions of nogoCS+ trials corresponded to a smaller PIT effect (i.e. PIT effect strength: Low $>$ Equal $>$ High). Post-hoc Wilcoxon tests showed that the PIT effect for the High group ($M = -5$ ms, $SD = 47$ ms) was significantly smaller than the Equal group ($M = -32.8$ ms, $SD = 58.6$ ms), $Z = 2.02$, $p = 0.04$, $d = 0.53$, and than the Low group ($M = -63$ ms, $SD = 68.6$ ms), $Z = 3.2$, $p = 0.001$, $d = 0.99$, though the difference between the Equal and Low groups did not reach statistical significance, $Z = 1.53$, $p = 0.13$, $d = 0.47$. Notably, the High group showed no evidence at all for a PIT effect ($Z = 0.04$, n.s.), while both the Equal and Low groups showed a significant PIT effect ($Z = 2.5$, $p = 0.01$, $d = 0.79$ and $Z = 3.8$, $p < 0.001$, $d = 1.3$, respectively) (Figure 2A). Moreover, ANOVAs showed no significant group differences for thirst level, juice rating, or “wanting” of the juice at any time throughout the experiment (i.e. upon arrival, before the Transfer phase, or after the Transfer phase), as well as no group differences in the overall number of presses (all P s > 0.05), indicating similar motivational drive for the juice reward across groups.

We also examined group differences for the PIT effect in a different way, using a linear regression with the proportion of nogoCS+ trials (40%, 25%, 10%) as the predictor variable and the PIT effect as the outcome variable. This showed that the group PIT effects scaled in a highly monotonic fashion with the proportion of nogoCS+ trials, $r = 0.999$, $p = 0.004$ (Figure 2A), again showing that the PIT effect decreased as the proportion of nogoCS+ trials increased (see Table 1 in Appendix for raw behavioral results during the Transfer phase).

We supposed that the monotonic relationship for the PIT effect across groups could be explained in three possible ways. First, nogoCS+ trials could represent a type of reward prediction error (i.e. the CS+ on that trial “prompts” the participant to expect juice but he/she is then denied it by performing a nogo). On this “reward prediction error” account, increased exposure to nogoCS+ trials throughout the Transfer phase could lead to a devaluation of the CS+ stimulus over time due to a gradual learning that the CS+ is no longer highly predictive of juice. Second, because a greater number of CS+ trials in the High

group were nogo trials (40% nogoCS+ vs. 25% goCS+), participants in the High group may have learned throughout the Transfer phase to pause responding upon seeing a CS+ stimulus, and vice-versa for CS- trials in the Low group. On this “pause” account, the reduction of the PIT effect in the High group thus merely reflects a different strategy to responding rather than an impact of having had to perform response suppression on nogoCS+ trials. Third, performing response suppression on nogoCS+ trials could lead to a transient increase in control mechanisms, whereby subsequent CS+ (compared to CS-) provocation is reduced to avoid a potentially inappropriate action. On this “control” account, CS+ provocation would be mitigated more frequently in groups with more nogoCS+ trials, resulting in a pattern of Low>Equal>High for the overall group PIT effect. Notably, reduced CS+ provocation in both the “reward prediction error” and “pause” accounts arises from learning new information about the CS+ throughout the Transfer phase, thus predicting stronger group differences in later blocks. On the other hand, reduced provocation in the “control” account does not necessarily depend on learning new information (because the change in the PIT effect is a direct consequence of having engaged response suppression on nogoCS+ trials, and this should emerge immediately). Instead, it predicts reduced CS+ provocation when following nogoCS+ (compared to nogoCS-) trials. Therefore, it might be possible to decide between these three accounts by analyzing the PIT effects in the three groups across the different blocks of the Transfer phase. If the PIT effect were reduced early on in the High group, then we would take this as preliminary evidence for the “control” account.

4.2.3. PIT effects across blocks—Due to normality violations, PIT effect values were log-transformed (specifically we used $\log(x+1)$ where x is the PIT effect in each participant; this accounts for negative values). These values were entered into a mixed-model ANOVA with Block (First/Second/Third) as a within-subject factor and Group (Low/Equal/High) as a between-subject factor. There was a main effect of Group ($F_{2,57} = 4.54$, $p = 0.01$), but no Block $\times$ Group interaction ($F < 1$, ns), indicating that group differences in the PIT effect did not differ across blocks. We followed up, as before, by running linear regression analyses, but now separately for each block. We found that the PIT effect reduced in the first block in the monotonic fashion of High > Equal > Low ($r = 0.99$) (Figure 2B). Because the monotonic effect was already present in block 1 (which only had 4, 10 and 16 nogoCS+ trials in the Low, Equal, and High groups, respectively), these results argue against the “reward prediction error” and “pause” accounts.

We followed the block analysis with a more stringent test of early versus late group differences by analyzing the PIT effect in first 20 and last 20 trials of the Transfer phase alone (Early and Late conditions, respectively). A mixed-model ANOVA with Time (Early/Late) as a within-subject factor and Group (Low/Equal/High) as a between-subject factor showed no significant Time $\times$ Group interaction ($F < 1$, ns), again demonstrating no learning effects across time. As these results provide evidence against the “reward prediction error” and “pause” accounts, we next sought to more directly test the “control” account.

4.3.4. Trial-by-trial analysis and results—The “control” account predicts trial-by-trial modulations of CS+ provocation; specifically, it predicts that CS+ provocation should be

reduced following nogoCS+ trials. We compared previous nogoCS+ to nogoCS- trials in order to eliminate any potential differences due to responding (“going”) versus not responding (“nogo-ing”) on the previous trial. We therefore analyzed first press RTs on current goCS+ and goCS- trials that followed either a correct nogoCS+ or nogoCS- trial. This yielded four trial types of interest: (1) nogoCS+,goCS+, (2) nogoCS-,goCS+, (3) nogoCS+,goCS-, (4) nogoCS-,goCS- (where the term before the comma represents trial t-1 and after the comma represents trial t). We collapsed the data across the three groups to increase statistical power and also because the High and Low groups had too few trials in some conditions to analyze separately (due to the varying proportions of nogoCS+ and nogoCS- trials). Collapsing across groups nearly equalized trial numbers at the aggregate level. Two participants had no observations in one or more cells and were therefore excluded from analysis. Because the data were non-normal ($W = 0.92$, $p < 0.001$), the RT values for the trial-by-trial analysis were log-transformed. These values were then entered into a repeated-measures ANOVA with Previous Trial (nogoCS+/nogoCS-) and Current Trial (goCS+/goCS-) as factors. For all analyses, we examined simple effects with non-parametric Wilcoxon tests when the original data were non-normal distributed, while t-tests were used when the original data were normally distributed. We therefore followed the ANOVA with planned contrasts using Wilcoxon signed rank tests.

ANOVA showed a significant main effect of Current Trial, $F_{1,57} = 14.98$, $p < 0.001$, with faster first press RT for goCS+ compared to goCS- trials (the PIT effect). There was also a trending Current Trial x Previous Trial interaction, $F_{1,57} = 2.28$, $p < 0.136$. Planned Wilcoxon signed rank tests revealed a significant difference in mean first press RT for nogoCS-,goCS+ ($M = 481$ ms, $SD = 103$ ms; $M_{\log\text{-value}} = -0.75$, $SD_{\log\text{-value}} = 0.2$) versus nogoCS-,goCS- ($M = 529$ ms, $SD = 123$ ms; $M_{\log\text{-value}} = -0.66$, $SD_{\log\text{-value}} = 0.21$), $Z = 3.16$, $p = 0.001$, $d = 0.47$; while, there was no difference for nogoCS+,goCS+ ($M = 496$ ms, $SD = 99$ ms; $M_{\log\text{-value}} = -0.72$, $SD_{\log\text{-value}} = 0.2$) versus nogoCS+,goCS- ($M = 519$ ms, $SD = 113$ ms; $M_{\log\text{-value}} = -0.68$, $SD_{\log\text{-value}} = 0.19$), $Z = 1.33$, n.s. (Figure 2C). This indicates that, following nogoCS- trials, there was strong provocation from the CS+ stimulus (compared to the CS- stimulus). However, following nogoCS+ trials, this provocation was no longer present. Focusing on CS+ trials alone, further analysis revealed slower first press RTs for nogoCS+,goCS+ compared to nogoCS-,goCS+ trials, $Z = 2.0$, $p = 0.045$, $d = 0.21$ (Figure 2C), showing that CS+ provocation was reduced when it was preceded by nogoCS+ versus nogoCS- trials.

4.2.5. Delta plot analysis and results—Our results thus far suggest that CS+ provocation is reduced following a putative enhancement of control mechanisms that follow nogoCS+ trials. To further test this, we compared RT delta plots of the High, Equal, and Low groups. Delta plots use RT distributions to try to reveal the putative temporal dynamics of activation/suppression processes in response tasks (Ridderinkhof, Scheres, Oosterlaan, & Sergeant, 2005; Ridderinkhof, 2002; Stürmer, Soetens, & Sommer, 2002). Specifically, one plots the RT difference between two conditions (in our case goCS+ and goCS-, the *delta* value) as a function of mean RT in different time bins. Regarding the temporal dynamics of activation/suppression, it is thought that suppression occurs when the slope of the delta values begins to level off or decrease as mean RT increases, while a linear increase in delta

values indicates little to no suppression (Ridderinkhof et al., 2005; van den Wildenberg et al., 2010; Wagenmakers, Grasman, & Molenaar, 2005). This predicts that, in the present study, the delta values (i.e. the PIT effect) will level off the most in the High group due to a larger proportion of suppressed goCS+ trials following nogoCS+ trials.

To construct the delta plots, RT distributions for correct goCS+ and goCS– trials were rank ordered and divided into five equal-sized bins in each participant (quantiles). We then calculated the difference score between the mean goCS+ and mean goCS– RT for each bin (i.e. the delta value). Unlike our previous analyses, we computed the differences score for goCS– minus goCS+ (instead of goCS+ minus goCS–), which is consistent with previous conflict studies that have computed delta values as incompatible minus compatible (i.e. slower minus faster responses) (e.g., Ridderinkhof, 2002). Next, we plotted these delta (PIT effect) values against the mean RT for each bin. Overall group differences in delta values were analyzed using a mixed-model ANOVA with Group (High/Equal/Low) as a between-subject factor and Bin (1/2/3/4/5) as a within-subject factor. As the delta values were non-normally distributed ($W = 0.78$, $p < 0.001$), they were first log-transformed, again using $\log(x+1)$ to correct for negative values.

ANOVA showed a significant main effect of Bin ($F_{4,228} = 6.84$, $p < 0.001$), with delta values increasing as a function of longer mean RTs. We also found a significant main effect of Group ($F_{2,57} = 5.15$, $p = 0.009$), with higher delta values for Low > Equal > High. Notably, there was a significant Bin x Group interaction ($F_{8,228} = 2.16$, $p = 0.03$), whereby the Low group showed a linear increase in delta values, while the delta values in the High group leveled off almost immediately (Figure 3A). The Equal group appeared to show a small increase in earlier bins (bins 1 and 2), followed by a larger increase in later bins (bins 4 and 5).

We followed the above analysis with an exploratory analysis that plotted mean delta slopes for each group in early time bins (bin1-bin2 and bin2-bin3) as a function of the proportion of nogoCS+ trials (Figure 3B). The delta slopes for the earliest phase, putatively corresponding to response activation (bin1-bin2), linearly scaled with the proportion of nogoCS+ trials, such that greater proportions of nogoCS+ trials were associated with smaller delta slopes.

4.3. DISCUSSION

We used the hybrid go-nogo/PIT task to test the hypothesis that response suppression over a motivationally-triggered action tendency (occurring on nogoCS+ trials) would reduce future CS+ provocation. We compared three groups that had different proportions of nogoCS+ trials, while we held the proportion of goCS+ and goCS– trials constant. We found that, across the three groups, the PIT effect decreased as the proportion of nogoCS+ trials increased in a highly monotonic fashion. We considered three potential accounts that could explain this result. The first was a “reward prediction error” account, in which the nogoCS+ trials could have induced a reward prediction error (since no juice was delivered despite the presence of the CS+), leading to a waning of the PIT effect as more nogoCS+ trials were encountered. The second was a “pause” account, where the participant could have learned over time that the CS+ background in the Transfer phase was more often associated with “nogo-ing” than “going”. This could have led to the emergence of a strategy of pausing

responding upon viewing a CS+. The third was a “control” account, whereby performing response suppression on nogoCS+ trials could have increased control mechanisms to reduce subsequent CS+ provocation and avoid a potential inappropriate provocation. The “control” account alone predicts mitigation of the CS+ following a nogoCS+ without any learning effects across time. We found that the group differences in the PIT effect emerged almost immediately and that there were no group differences in the PIT effect across blocks or even when comparing the first versus the last twenty trials, thus providing support for the “control” account.

We also tested the “control” account prediction that CS+ provocation would be reduced following nogoCS+ trials by examining the current trial (goCS+/goCS-) as a function of the previous trial type (nogoCS+/nogoCS-). We found that first press RTs for goCS+ trials (but not goCS- trials) were significantly slower when the previous trial was a nogoCS+ compared to a nogoCS-. This slowing eliminated the PIT effect when the previous trial was nogoCS+, while the PIT effect remained strong when the previous trial was nogoCS-. It is therefore likely that this reduced CS+ provocation manifested in an overall reduced PIT effect as the number of nogoCS+ trials increased.

Finally, we used delta plots to further test the hypothesis that nogoCS+ trials led to a putative enhancement of control mechanisms that reduced subsequent goCS+ provocation. We found that while the Low group showed a linear increase in the PIT effect as a function of mean RT, the PIT effect quickly leveled off in the High group. We interpret this as the sign of a response suppression control mechanism (Ridderinkhof et al., 2005). Consistent with this, a closer examination of the very earlier time bins showed that the higher the proportion of nogoCS+ trials, the smaller the delta slope. This again suggests that a putative response suppression following nogoCS+ trials reduced the early CS+ provocation. Taken together, these results lend support to the “control” account, whereby nogoCS+ trials engage a response control mechanism that reduces CS+ provocation on the subsequent trial, while leaving subsequent CS- trials unaffected.

5. EXPERIMENT 2

Above we showed that nogoCS+ trials (compared to nogoCS- trials) led to a decrease in the provocation generated by the CS+ on the following trial, while leaving the CS- unaffected. We now aimed to replicate and extend this. We re-analyzed behavioral data from the paper by Freeman et al., 2014, which had a near-identical design. We again tested whether nogoCS+ trials (compared to nogoCS- trials) led to a decrease in the provocation generated by the goCS+ on the following trial. In addition, as that study included neurophysiological data from the single-pulse TMS procedure, we re-analyzed those data as well. As explained in the Introduction, spTMS provides a high temporal resolution index of the overall corticospinal excitability for a particular muscle. On each trial, the single pulse was delivered at 250 ms after the stimulus (go or nogo CS+ or CS-), which was approximately 300 ms before the average response was made on go trials. This allowed us to “visualize” activation and suppression processes for goCS+ and goCS- trials several hundred milliseconds before the motor response itself. Based on results from Experiment 1, we predicted reduced MEPs for goCS+ trials when the previous trial was nogoCS+ versus

nogoCS–; whereas, for goCS– trials, we predicted MEPs would be unaffected by the previous trial type.

5.1. METHOD

5.1.1. Participants—Seventeen participants (eleven female) were tested (mean age = 20.59, SD = 2.4). Two were excluded for having oversaturated motor evoked potentials (MEPs) (i.e. MEPs > 2 mV), and one was excluded because mean normalized MEPs were greater than 3 SD from the group mean. Thus, all analyses for Experiment 2 were run on 14 participants, as in Freeman et al. (2014). All participants provided IRB consent and passed TMS safety screening.

5.1.2. Stimuli and procedure—The task design, stimuli, and procedure were identical to Experiment 1, with the following exceptions: i) there was only one group, which had equal proportions for all trial types (just like the Equal group in Experiment 1), ii) there were now 4 blocks of 50 trials (200 total), iii) the trial duration for the Instrumental and Transfer phases was 3.5 s, iv) spTMS was applied during the experiment, and v) 1/5 of all trials were Null baseline trials for normalization of the MEP (see Freeman et al., 2014 for more details).

5.1.3. TMS procedure details—TMS was delivered using a MagStim 200–2 system (MagStim, Whitland, UK) and a 70 mm figure-of-eight coil. Surface EMG was recorded from the first dorsal interosseous (corresponding to the task-relevant index finger) and the abductor digiti minimi (corresponding to the task-irrelevant pinky finger) muscles of the right hand (Figure 1C) via 10-mm-diameter Ag-AgCl hydrogel electrodes (Medical Supplies Inc., Newbury Park, CA).

The coil was placed 5 cm lateral and 2 cm anterior to the vertex and repositioned while delivering a TMS stimulus to locate the position where the largest MEPs were observed consistently. We measured resting motor threshold, defined as the minimum stimulation intensity required to induce 0.1 mV peak-to-peak amplitude MEP in 5 out of 10 consecutive stimulations (Rossini et al., 1994). Next, the maximum MEP size was determined by increasing stimulus intensity in 3–4% increments until the MEP amplitude no longer increased. Finally, the TMS stimulus intensity was adjusted to produce a MEP that was approximately half of the maximum MEP amplitude while the participant was performing the task in a practice session. This was the intensity used during the experiment proper (mean intensity across participants was 46.64% stimulator output, SD = 9.34). For every trial, a TMS pulse was delivered 250 ms after the onset of the stimulus. For all TMS experiments (Experiments 2–4), the right index finger moved inward to press a vertical key, which is optimal for EMG recording over the FDI muscle.

5.1.4. Behavioral analysis—RT values were normally distributed ($W = 0.99$, $p > 0.05$). As in our trial-by-trial analysis for Experiment 1, we used repeated-measures ANOVA to examine first press RT for the factors of Previous Trial (nogoCS+/nogoCS–) and Current Trial (CS+/CS–). Because the data were normally distributed, planned comparisons were made using two-tailed, paired t-tests.

5.1.5. Motor evoked potential (MEP) analysis—An EMG sweep started 400 ms before stimulation. MEPs were identified from the EMG using in-house software developed in Matlab (Mathworks, Natick, MA). Trials were excluded if the root mean square EMG in the 100 ms before the TMS pulse was greater than 0.01 mV, if the MEP was less than 0.05 mV, or if the amplitude maxed out at 2 mV. Mean peak-to-peak amplitudes of MEPs were calculated for all conditions. Mean MEPs for each condition were normalized by the mean MEP of the Null trials (see Freeman et al., 2014 for details). This was done for the FDI and ADM muscles separately; however, our analysis focuses on the task-relevant FDI muscle. As MEP values were non-normally distributed ($W = 0.91$, $p < 0.001$), we log-transformed the MEP values and then entered them into a repeated-measures ANOVA with Previous Trial (nogoCS+/nogoCS-) and Current Trial (goCS+/goCS-) as factors. Planned comparisons were made using two-tailed Wilcoxon signed rank tests.

5.2. RESULTS

5.2.1. Behavior—For first press RTs, ANOVA revealed a significant main effect of Current Trial, $F_{1,13} = 11.86$, $p = 0.004$, with faster first press RTs for goCS+ compared to goCS- trials (the PIT effect). There was also a significant Previous Trial x Current Trial interaction, $F_{1,13} = 4.87$, $p = 0.046$, in which the PIT effect was present when the previous trial was nogoCS-, but not nogoCS+. Planned t-tests showed significantly faster RTs for nogoCS-,goCS+ ($M = 521$ ms, $SD = 54$ ms) compared to nogoCS-,goCS- ($M = 584$ ms, $SD = 70$ ms), $t_{13} = 3.47$, $p = 0.002$, $d = 0.9$, yet no difference between nogoCS+,goCS+ ($M = 564$ ms, $SD = 82$ ms) and nogoCS+,goCS- ($M = 571$ ms, $SD = 56$ ms), $t_{13} < 1$, n.s. (Figure 4A). We also found significantly slower first press RTs for nogoCS+,goCS+ compared to nogoCS-,goCS+ trials, $t_{13} = 2.23$, $p = 0.009$, $d = 0.83$ (Figure 4A). This pattern of results replicates the trial-by-trial findings from Experiment 1 by demonstrating reduced CS+ provocation following nogoCS+ trials, while leaving CS- RTs on the current trial unaffected by the previous trial type (see Table 2 in Appendix for raw behavioral results during the Transfer phase).

5.2.2. MEP—ANOVA revealed a significant main effect of Current Trial, $F_{1,13} = 5.00$, $p = 0.04$, with higher MEPs for goCS+ compared to goCS- trials. We also found a marginally significant Previous Trial x Current Trial interaction, $F_{1,13} = 3.64$, $p = 0.08$, which showed higher MEPs for goCS+ compared to goCS- trials only when the previous trial type was nogoCS-. Planned Wilcoxon tests revealed significantly higher MEPs for nogoCS-,goCS+ ($M = 1.24$ mV, $SD = 0.53$ mV; $M_{\log\text{-value}} = 0.13$ mV, $SD_{\log\text{-value}} = 0.42$ mV) compared to nogoCS-,goCS- ($M = 0.92$ mV, $SD = 0.30$ mV; $M_{\log\text{-value}} = -0.13$ mV, $SD_{\log\text{-value}} = 0.34$ mV), $Z = 2.23$, $p = 0.026$, $d = 0.7$, yet no difference between nogoCS+,goCS+ ($M = 0.94$ mV, $SD = 0.31$ mV; $M_{\log\text{-value}} = -0.11$ mV, $SD_{\log\text{-value}} = 0.30$ mV) and nogoCS+,goCS- ($M = 1.01$ mV, $SD = 0.34$ mV; $M_{\log\text{-value}} = -0.04$ mV, $SD_{\log\text{-value}} = 0.34$ mV), $Z = 0.72$, n.s. (Figure 4B). Thus, evidence for the PIT effect (greater MEPs for goCS+ versus goCS-) was seen when the previous trial was nogoCS-, but not when the previous trial was nogoCS+. We also found marginally reduced MEPs for nogoCS+,goCS+ versus to nogoCS-,goCS+ ($Z = 1.91$, $p = 0.056$, $d = 0.52$) (Figure 4B), again pointing to the influence of the previous trial type on subsequent CS+ provocation. These results corroborate the behavioral findings from Experiments 1 and 2 by showing that nogoCS+ (compared to nogoCS-) trials

influenced MEPs on the following trial if a CS+, but not a CS–, was present (see Table 3 in Appendix for raw MEP results).

We also examined root mean square (RMS) EMG for the 100 ms time window before the TMS pulse to determine if the above results were contaminated by differences in the pre-TMS period. An ANOVA for the normalized RMS values showed no significant main effects or interactions (all P s > 0.22), demonstrating no pre-pulse contamination.

5.3. DISCUSSION

We re-analyzed behavioral data from a paradigm almost identical to Experiment 1. We show again that CS+ provocation was reduced following nogoCS+ trials, while CS– was unaffected by the previous trial type. We also re-analyzed MEP data from 250 ms post-stimulus. Consistent with the behavioral results, we found reduced CS+ provocation following nogoCS+ trials. This shows that the motor provocation (measured at 250 ms) was diminished long before a response was made (~550 ms). This suggests that the slower first press RT result was not due to slower execution of the response (as a response would not even be initiated that early), but instead due to reduced motor provocation elicited by the CS+, most likely via a response control mechanism.

Experiment 2 substantiates the finding that response suppression over a motivationally-triggered action tendency leads to reduced CS+ provocation; yet, it is unclear if CS+ provocation is down-modulated after an initial burst of motor excitation (i.e. after a few hundred milliseconds), or if the CS+ is prevented from exciting the motor system in the first place. If the latter were true, it would suggest that early CS+ provocation is mitigated by a response control mechanism that is already in place before the onset of the trial. This predicts that the “suppression” effect should be visible very early, even within 100 ms post-stimulus onset. We tested this in a new experiment.

6. EXPERIMENT 3

We used the same behavioral paradigm as before, but now measured MEPs 100 ms after stimulus onset (instead of 250 ms in Experiment 2). Measuring MEPs at this early time point allowed us to investigate early motor excitation elicited by the CS+ (compared to the CS–) stimulus. Greater CS+ activity at this early time point would indicate that CS+ activity is down-modulated following nogoCS+ trials once it has already energized the motor system. This would suggest a form of reactive control, whereby motor excitation is suppressed (possibly around 250 ms based on Experiment 2) after an early provocation from the CS+. On the other hand, reduced CS+ activity at this early time point would suggest that a control mechanism is already in place after nogoCS+ trials to prevent any significant motor energization by the CS+.

6.1. METHOD

6.1.1. Participants—Sixteen participants (eleven female) were tested (mean age = 20.15, SD = 2.2). Three participants were excluded for having oversaturated MEPs (i.e. MEPs > 2 mV). Thus, all analyses for Experiment 3 were run on 13 participants. All participants provided IRB consent and passed TMS safety screening.

6.1.2. Stimuli and procedure—The task design, stimuli, and procedures were identical to Experiment 2, with the following exceptions: i) there were 2 blocks of 48 trials, ii) 1/3 of all trials were Null trials, iii) the response duration was reduced from 3.5 s to 3 s, iv) EMG recordings were only taken from the FDI muscle, and v) the TMS pulse was delivered 100 ms after stimulus onset. The total of 96 trials was considerably less than the 200 trials used in Experiment 2. This was done as we learned that the PIT effect wanes across time (Freeman et al., 2014). The mean TMS intensity across participants was 49.58% stimulator output, $SD = 8.77$.

6.1.3. MEP analysis—MEPs for go and nogo trials have been shown to diverge around 150 ms following stimulus onset (Coxon, Stinear, & Byblow, 2006; Hoshiyama et al., 1997; Yamanaka et al., 2002). Here, we pulsed at 100 ms after stimulus onset, which is about 50 ms before go and nogo MEPs were likely to diverge. Therefore, go and nogo MEPs on the current trial were collapsed. This yielded four trial types: (1) nogoCS+,CS+, (2) nogoCS−,CS+, (3) nogoCS+,CS−, (4) nogoCS−,CS−. MEP values were non-normally distributed (Shapiro-Wilk test: $W = 0.78$, $p < 0.001$). We therefore log-transformed the MEP values. To test for differences in MEPs, we used a repeated-measures ANOVA with Previous Trial (nogoCS+/nogoCS−) and Current Trial (goCS+/goCS−) as factors. Planned comparisons were made using two-tailed Wilcoxon signed rank tests. We also used one-tailed (due to the strong directional prediction), paired t-tests to examine conditioning during the Pavlovian phase (CS+ versus CS−) and the overall PIT effect (goCS+ versus goCS−). There were insufficient trial numbers in each condition to examine trial-by-trial behavioral effects on go trials. Thus, our trial-by-trial results focused on the MEP analysis.

6.2. RESULTS

We verified that conditioning took place during the Pavlovian phase, evidenced by significantly faster RTs for CS+ compared to CS− trials, $t_{12} = 3.25$, $p = 0.004$, $d = 0.9$. We also verified that a behavioral PIT effect was indeed present in the Transfer phase, shown by significantly faster first press RTs for goCS+ compared to goCS− trials, $t_{12} = 2.93$, $p = 0.006$, $d = 0.81$ (see Table 2 in Appendix for raw behavioral results during the Transfer phase). Next, we verified that MEPs on go and nogo trials did not show significant divergence at 100 ms after stimulus onset (paired t-test: $t_{12} < 1$, n.s.). This is consistent with prior studies (Coxon et al., 2006; Hoshiyama et al., 1997; Yamanaka et al., 2002) and justifies our collapsing across go and nogo trials.

For the trial-by-trial MEP analysis, ANOVA revealed no significant main effect of Previous Trial ($F_{1,12} < 1$, n.s.) or Current Trial ($F_{1,12} < 1$, n.s.). However, there was a nearly significant Previous Trial x Current Trial interaction, $F_{1,12} = 4.63$, $p = 0.052$. Wilcoxon tests showed that MEPs for nogoCS+,CS+ ($M = 0.84$ mV, $SD = 0.46$ mV; $M_{\log\text{-value}} = -0.36$ mV, $SD_{\log\text{-value}} = 0.73$ mV) were significantly reduced compared to both nogoCS−,CS+ ($M = 1.18$ mV, $SD = 0.63$ mV; $M_{\log\text{-value}} = 0.05$ mV, $SD_{\log\text{-value}} = 0.49$ mV), $Z = 2.06$, $p = 0.04$, $d = 0.48$, and nogoCS+,CS− ($M = 1.25$ mV, $SD = 0.97$ mV; $M_{\log\text{-value}} = 0.07$ mV, $SD_{\log\text{-value}} = 0.51$ mV), $Z = 2.2$, $p = 0.03$, $d = 0.65$ (Figure 5). Notably, because CS− trials were not influenced by previous nogoCS+ trials (as seen in Figures 2C and 4A–B), the latter result suggests that motor activity on CS+ trials was suppressed (i.e. prevented from normal

motor energization) when following nogoCS+ trials (Figure 5; see Table 4 in Appendix for raw MEP results).

Again, an examination of the normalized RMS values for the 100 ms time window before the TMS pulse showed no significant main effects or interactions (all P s > 0.28), demonstrating that the above results were not contaminated by differences in the pre-TMS period.

6.3. DISCUSSION

Experiment 3 showed that response suppression over a motivationally-triggered action tendency led to reduced CS+ provocation on the subsequent trial a mere 100 ms after stimulus onset. This is supported by the significantly lower MEPs for nogoCS+,CS+ trials compared to both nogoCS-,CS+ and nogoCS+,CS- trials. Because CS- trials appear to be unaffected by previous nogoCS+ trials (Figure 5), we interpret this reduction as a suppressive influence over the CS+ to prevent motor provocation. Notably, these results argue against the hypothesis that, following nogoCS+ trials, presentation of a CS+ leads to quick motor excitation that then triggers reactive response suppression, and instead support the hypothesis that a control mechanism is already in place to prevent CS+ provocation. This interpretation is based on the timing of the suppression, which is likely too early to become engaged in a reactive manner following early CS+ provocation (Coxon et al., 2006; Yamanaka et al., 2002). Instead, the suppressive effect we observed at 100 ms is more likely to result from a mechanism that is already in place before the onset of the trial and that becomes activated once a CS+ is detected. In Experiment 4, we more directly tested this hypothesis by delivering TMS pulses before the trial onset.

7. EXPERIMENT 4

Here we used the same behavioral paradigm as Experiments 1–3, but this time TMS pulses were delivered 500 ms prior to stimulus onset (during the ITI period). This time point allowed us to examine if a putative response suppression mechanism was engaged before the onset of the next trial when following nogoCS+ compared to nogoCS- trials. As we had previously shown that response suppression during this task was selective to the task-relevant FDI muscle (index finger) (Freeman et al., 2014), we supposed that the response suppression mechanism for the trial-by-trial effects would also be selective to the FDI muscle. Thus, we simultaneously recorded from the FDI (index finger) and ADM (pinky finger) muscles. We used the ADM as a baseline measurement to provide an index of selective FDI suppression that is not confounded by mere differences in non-specific arousal/tone (since those differences should be reflected in both muscles).

7.1. METHOD

7.1.1. Participants—Twenty-two participants (14 female) were tested (mean age = 20.52, SD = 3.4). Four participants were excluded for having greater than 50% invalid trials in a condition of interest (i.e. the MEPs were oversaturated or less than 0.05 mV). One participant was excluded for wishing to be withdrawn from the procedure. Thus, all analyses

for Experiment 4 were run on 17 participants. All participants provided IRB consent and passed TMS safety screening.

7.1.2. Stimuli and procedure—The task design, stimuli, and procedures were identical to Experiment 2, with the following exceptions: i) there were 2 blocks of 52 trials, ii) there were no Null trials, since the ADM muscle was to serve as a baseline comparison, iii) the response duration was 3 s (as in Experiment 3), and iv) the TMS pulse was delivered 500 ms before stimulus onset (during the ITI period). Pulses were delivered on 60% of trials, chosen pseudorandomly to ensure all trial types were matched for number of pulses. This rate of pulsing reduced the chance that participants would strategically wait for the pulse as an indication of trial onset, while providing sufficient trial numbers for analysis. The mean TMS intensity across participants was 49.18% stimulator output, SD = 9.21.

7.1.3. MEP analysis—For each participant, difference scores were computed for mean MEPs in the FDI and ADM muscles. This was done for pulses delivered after nogoCS+ and nogoCS– trials, thus providing an index of selective suppression of the FDI muscle that is not confounded by general differences in arousal.

MEP values were normally distributed ($W = 0.97$, $p > 0.05$). Therefore, paired t-tests were used to examine the PIT effect (goCS+ versus goCS–) and MEP differences following nogoCS+ and nogoCS– trials. These tests were one-tailed due to the strong directional predictions. We also predicted higher FDI scores overall, since the FDI is a larger muscle that generally evokes larger MEPs compared to the ADM.

7.2. RESULTS

Again, we found both a significant conditioning effect for CS+ versus CS– during the Pavlovian phase ($t_{17} = 3.34$, $p = 0.002$, $d = 0.81$), as well as a behavioral PIT effect ($t_{17} = 1.83$, $p = 0.04$, $d = 0.44$), shown by significantly faster RTs for goCS+ compared to goCS– trials (see Table 2 in Appendix for raw behavioral results during the Transfer phase). Of main interest was the MEP analysis for the time-point 500 ms before stimulus presentation. We found that MEPs were significantly lower following nogoCS+ (FDI minus ADM score: $M = 0.19$ mV, $SD = 0.15$ mV) compared to nogoCS– (FDI minus ADM score: $M = 0.24$ mV, $SD = 0.18$ mV) trials, $t_{16} = 1.90$, $p = 0.038$, $d = 0.46$ (Figure 6). This was due to changes in the FDI (nogoCS+: $M = 0.46$ mV, $SD = 0.17$ mV; nogoCS–: $M = 0.50$ mV, $SD = 0.22$ mV) and not to the ADM (nogoCS+: $M = 0.27$ mV, $SD = 0.14$ mV; nogoCS–: $M = 0.26$ mV, $SD = 0.15$ mV). We interpret this as suppression in the FDI muscle following nogoCS+ compared to nogoCS– during the ITI period (Figure 6; see Table 5 in Appendix for raw MEP results). These results were not contaminated by differences in the pre-TMS period, as the RMS values for the FDI-ADM in the 100 ms time window before the TMS pulse showed no significant difference between the nogoCS+ and nogoCS– conditions ($t_{17} = 1.1$, n.s.).

7.3. DISCUSSION

We delivered TMS in the ITI period 500 ms before trial onset to analyze MEPs as a function of prior trial. As for the above experiments, we recorded from the FDI muscle, but also here

from the ADM muscle as a control condition for mere motor changes reflecting arousal/difficulty/attention. We found that MEPs during the ITI period in the task-relevant FDI muscle (relative to the ADM muscle) were indeed reduced following nogoCS+ compared to nogoCS- trials. In line with our prediction, this reduction was due to changes in the FDI and not the ADM. These results provide evidence that nogoCS+ trials engage a response suppression mechanism that is already in place before the next trial occurs.

8. GENERAL DISCUSSION

We examined if and how response suppression over a motivationally-triggered action tendency influences future provocation of a Pavlovian (CS+) stimulus. In Experiment 1, we tested this by varying the number of times that such response suppression was recruited (i.e. by varying the proportion of nogoCS+ trials between groups) and examined if this manipulation would influence CS+ provocation. We found that varying the number of nogoCS+ trials had a profound influence on the PIT effect (goCS+ versus goCS-). This was reflected in a highly monotonic relationship between the proportion of nogoCS+ trials and the group PIT effect, whereby groups with a higher proportion of nogoCS+ trials exhibited a decreased PIT effect. Further analysis showed that nogoCS+ (compared to nogoCS-) trials led to a reduction in quick motor provocation (evident in slower first press RTs) if a CS+, but not a CS-, occurred on the following trial. The delta plot analysis was also consistent with this: groups with a high proportion of nogoCS+ trials had the smallest early response activation. Together, these results suggest that a response control mechanism is transiently engaged following nogoCS+ trials to mitigate potential CS+ provocation on the next trial.

In Experiment 2, we replicated the trial-by-trial effects observed in Experiment 1, and also found the same pattern for physiological motor excitability: goCS+ trials following nogoCS+ trials had reduced MEPs 250 ms after stimulus onset. This early MEP difference, which was several hundred milliseconds before the response, indicates that the slower first press RT result is indeed because of reduced motor provocation elicited by the CS+ rather than slower execution of the response itself.

Experiment 3 extended the findings from Experiments 1 and 2 by showing that, when preceded by a nogoCS+ (compared to a nogoCS-) trial, MEPs for the CS+ stimulus were reduced a mere 100 ms after stimulus onset. Moreover, when following nogoCS+ trials, MEPs for the CS+ were even significantly lower than for the CS-, pointing to a suppressive influence that prevents normal motor energization of a stimulus with motivational drive (i.e. the CS+). This suppressive influence is likely not reactively triggered by rising activation generated by the CS+, since 100 ms is presumably too fast for such activation/suppression to occur. Instead, these results suggest that a control mechanism was already in place prior to trial onset to prevent any CS+ provocation from occurring.

Experiment 4 showed significantly reduced MEPs following nogoCS+ versus nogoCS- trials during the ITI period in the task-relevant FDI muscle relative to ADM. This substantiated the hypothesis that a response suppression mechanism is already in place following nogoCS+ trials.

8.1. Motivationally-triggered response suppression has subsequent effects in mitigating provocation

Taken together, our results converge to suggest that, following nogoCS+ trials, a control mechanism is transiently in place to prevent the CS+ from provoking the motor system. Notably, nogoCS+ trials had apparently no influence on subsequent CS– trials. This suggests that the observed effects were not due to a general motor slowing, which would likely influence CS+ and CS– trials to the same extent. Instead, our results indicate that, following nogoCS+ trials, CS+ provocation is prevented from energizing the motor system through a suppressive mechanism.

From the results of the present study, it is not clear if the putative control mechanism in this study was present as a result of lingering response suppression on nogoCS+ trials, or if it became re-engaged after nogoCS+ trials (i.e. in the ITI period) in a top-down manner. However, based on the specificity of the suppressive effects to the CS+ stimulus, we favor the “re-engagement” over the “lingering” explanation. This is because a “lingering” explanation suggests that the observed effects are merely a by-product of implementing response suppression over a motivationally-triggered action tendency, and should therefore affect subsequent CS+ and CS– energization to a similar extent. Yet, here, the response suppression appears to be more goal-directed since only the CS+ was targeted. Thus, we hypothesize that nogoCS+ trials leads to a re-engagement of top-down (though not necessarily conscious) control by placing the task-relevant effector in a suppressed state. If a CS+ occurs on the following trial, the suppressed state prevents motivational provocation. If, however, a CS– occurs on the following trial, the response suppression is most likely released (Burle, Vidal, Tandonnet, & Hasbroucq, 2004; van Campen, Keuken, van den Wildenberg, & Ridderinkhof, 2013; see Figure 7). We also speculate that, due to the apparent “proactive” element of the response control in the current study (shown in Experiments 3 and 4), the neural mechanisms that help prevent CS+ provocation would resemble the proactive fronto-striatal circuits involved in proactively stopping a motor response, including the presupplementary motor area, ventrolateral prefrontal cortex, and the striatum (Majid, Cai, Corey-Bloom, & Aron, 2013; Zandbelt, Bloemendaal, Neggens, Kahn, & Vink, 2013). Future experiments could directly test this hypothesis with careful experimental designs that separate the “proactive” ITI period from the onset of the next trial.

8.2. Relation to the classic conflict adaptation effects

The current results resemble conflict adaptation effects that have been well documented for classic cognitive psychology tasks, such as the flanker (Eriksen & Eriksen, 1974), Stroop (Stroop, 1935), and Simon tasks (Simon, 1967; Botvinick, Cohen, & Carter, 2004; Chen & Melara, 2009; Egner & Hirsch, 2005; Ullsperger, Bylsma, & Botvinick, 2005). In these experiments, trials are considered to be “high-conflict” if there is incongruity between automatic response tendencies and task goals (e.g., in the Simon task, responding with the right hand to a blue circle when the circle appears on the left side of the screen; see Botvinick, Cohen, & Carter, 2004). Such studies have consistently found that congruency effects are smaller if they follow a high conflict (i.e. incongruent/incompatible) versus a low conflict (congruent/compatible) trial—a finding first referred to as the “Gratton effect” (Gratton et al., 1992; Egner, 2007). It has been argued that this is due to an augmentation of

cognitive control mechanisms that can monitor for and reduce potential conflict (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Botvinick et al., 2004; Chen & Melara, 2009; Egner, 2007; but see Mayr, Awh, & Laurey, 2003; Nieuwenhuis et al., 2006 for a perceptual priming account). This can be accomplished either by enhancing attentional focus towards the target and away from the distractor stimuli, as in the Stroop task (Botvinick et al., 2004; Egner & Hirsch, 2005a; Egner & Hirsch, 2005b; Egner, 2007; Kerns et al., 2004, but see Cohen Kadosh, Gevers, & Notebaert, 2011), or by putatively suppressing unwanted response tendencies, as in the Simon and Flanker tasks (Burle, Spieser, Servant, & Hasbroucq, 2014; Burle et al., 2004; van Campen et al., 2013; Pratte, Rouder, Morey, & Reng, 2010; Stürmer, Soetens, & Sommer, 2002).

In the present study, one could conceptualize nogoCS+ trials as “high-conflict” due to inappropriate response activation when a response requires withholding; whereas, on nogoCS– trials, inappropriate response activation is not generated (due to the equal proportion of go and nogo trials inducing minimal prepotency), likely resulting in a low amount of conflict. In this framework, reduced CS+ provocation following high-conflict nogoCS+ trials resembles the types of conflict adaptation mentioned above for the Simon and Flanker tasks, where response suppression mechanisms are thought to modulate automatic response tendencies following incompatible trials (Burle et al., 2004; van Campen et al., 2013; Klein, Petitjean, Olivier, & Duque, 2013). However, from these studies, it is unclear if such control mechanisms could at all influence Pavlovian-induced response activation that drives an action towards a reward. Our results show that a response suppression mechanism can indeed influence motivationally-triggered provocations by becoming engaged prior to the potential provocation and preventing it from ever taking place. This suggests that conflict adaptation effects observed in previous conflict adaptation studies may involve a common control system that is recruited independently of the source of activation. Therefore, our results both substantiate the potential translational value of traditional cognitive psychology paradigms and provide a foundation for exploring how control mechanisms interact with motivationally-triggered response activation.

8.3. Limitations

There are several limitations and remaining questions that should be addressed. First, these experiments only provide a coarse view of the underlying dynamics of activation and suppression. For example, Experiment 4 could only sample one time-point in the ITI period. This is due to a limitation of the current go-nogo/PIT paradigm, which is that the PIT effect wears off across time. One future direction would be to elicit non-diminishing motivational provocation by re-establishing these effects with monetary reward and a task-relevant Pavlovian cue that indicates the amount of money one could potentially earn on a given trial. This could allow experiments with high trial numbers, thus lend such experiments to mapping the temporal dynamics of activation/suppression. Future experiments could also try to better visualize such dynamics using a continuous measure such as electroencephalography.

A second limitation of this study is that it does not explain exactly why individuals apparently engaged and re-engaged (or maintained) a response suppression mechanism

several seconds following nogoCS+ trials. Moreover, it is unclear how long the effect lasts (only into the next trial or longer into the future), since the intervening trial types would confound analyzing beyond one trial in the current experiments. Future experiments could potentially address this question by manipulating ITI durations. One might expect, for example, that a lingering process—but not necessarily a re-engagement mechanism—would show the strongest effects at very short ITIs. Finally, it is unclear if this effect was an automatic or deliberate consequence of having just done response suppression. One possibility to be explored in future studies is that withholding a motivated response is aversive, which led participants to deliberately engage a control mechanism that prevented motivational provocation shortly thereafter.

9. Conclusions and Implications

We show that increasing the number of times that response suppression over a motivationally-triggered action tendency is implemented leads to decreased motor provocation by a Pavlovian stimulus, reflected in a smaller PIT effect. In a series of follow-on analyses and experiments, we showed that this reduction was instantiated by a response suppression mechanism that followed nogoCS+ trials and prevented subsequent provocation of the Pavlovian stimulus. We propose that this control mechanism arose from a re-engagement of the control mechanism previously observed on nogoCS+ trials (Freeman et al., 2014) to proactively suppress subsequent CS+ provocation. Our results resemble classic conflict adaptation effects with traditional conflict tasks (i.e. Simon and flanker tasks). This raises the prospect that suppressing/preventing response activation after conflict involves a common control system. Thus, developing a better understanding of the underlying control mechanisms in traditional tasks could have significance for the reward-driven provocations that we commonly encounter in everyday life. It is also possible that a better mechanistic understanding of how inappropriate response activation is prevented could be practically useful. For example, it could give insight into training people to prevent the potentially maladaptive influences of Pavlovian stimuli (Cavanagh et al., 2013; Chiu et al., 2014; Dayan et al., 2006; van Loon, van den Wildenberg, van Stegeren, Hajcak, & Ridderinkhof, 2010). Perhaps people could learn to voluntarily harness this putative control mechanism, even in an extended manner when faced with a situation where an appetitive Pavlovian stimulus might provoke action tendencies that conflict with their long-term goals. Here we set the stage for such studies by demonstrating that suppressing a motivationally-triggered action tendency diminishes future Pavlovian provocation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by a US National Institutes of Health Grant DA026452 to A.R.A. and by a National Science Foundation Graduate Research Fellowship to S.M.F.

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Highlights

- We studied how suppressing a motivated action affects Pavlovian-induced provocation
- CS+ provocation decreased with more frequent suppression of motivated action
- Such suppression inculcated a control mechanism that prevented CS+ provocation
- Harnessing this mechanism could reduce maladaptive effects of Pavlovian stimuli

Figure 1.

Go-nogo/Pavlovian-to-instrumental transfer (PIT) task. (A) In the Instrumental phase, participants continuously pressed with the right index finger to obtain juice on go (square) trials. Juice delivery was based on a variable ratio reward schedule. On nogo (triangle) trials, no press was to be made; else an error message was displayed (not shown here). In the Pavlovian phase, participants made speeded button presses with the left hand to indicate the location (left or right) of the colored rectangle. Juice was always delivered for the CS+ color (shown as green here) and was never delivered for the CS- color (shown as purple here).

The Transfer phase was identical to the Instrumental phase, except that the Pavlovian colors (rather than gray) appeared in the background. (B) Transfer phase trial type proportions. The proportion of goCS+ and goCS- trials were the same across all groups. The proportion of nogoCS+ to nogoCS- trials was 4:1 in the High Group, 1:1 in the Equal Group, and 1:4 in the Low Group. (C) Experimental setup. For Experiments 2–4, TMS was applied over the left primary motor cortex. In Experiments 2 and 4, electromyography was recorded simultaneously from the index and pinky fingers of the right hand; while, in Experiment 3, only the index EMG was recorded.

Figure 2.

Experiment 1 results. (A) Group PIT effects. The “PIT effect” represents mean goCS+ trials minus mean goCS– trials for first press RT in the Transfer phase. Across groups, a decrease in the percentage of nogoCS+ trials corresponds to an increase in the group PIT effect. (B) Relationship of group PIT effect and proportion of nogoCS+ trials in each block of the Transfer phase. The monotonic relationship in 2A is already present in the first block. (C) Behavioral trial-by-trial results. Mean first press RTs are collapsed across High, Equal, and Low groups. The pattern shows significantly slower RTs for goCS+ trials when following nogoCS+ (compared to nogoCS–) trials. There appears to be no influence of previous trial type on current goCS– trials. Mean RTs are shown but were log-transformed for statistical analyses due to normality violations. Error bars represent the SEM across participants. **** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

Figure 3.

Delta plots and early delta slopes from Experiment 1. (A) The delta RT (goCS- minus goCS+) is plotted against the mean RT for five time bins. Delta plots were significantly different across groups, with the High group showing evidence for response suppression on go trials. (B) Delta slope for the earliest time bins (bin1-bin2) across groups. There was a monotonic relationship between the delta slope and the proportion of nogoCS+ trials; specifically, a higher proportion of nogoCS+ trials was associated with less early response activation.

Figure 4.

Experiment 2 behavior and TMS. (A) First press RTs on current go trials as a function of previous trial type. RTs for goCS+ trials were significantly slower when following nogoCS+ (compared to nogoCS-) trials, replicating the trial-by-trial results in Experiment 1. (B) MEPs on current trial as a function of previous trial type at 250 ms after stimulus onset in the task-relevant FDI muscle. MEPs for goCS+ trials were marginally significantly reduced ($p = 0.056$) 250 ms after stimulus onset (approximately 300 ms before mean first press RT) when following nogoCS+ (compared to nogoCS-) trials. Similar to the behavior in Experiments 1 and 2, goCS- trials were unaffected by previous trial type. MEPs are shown normalized by baseline but were log-transformed for statistical analyses due to normality violations. Error bars represent the SEM across participants. $**p < 0.01$, $*p < 0.05$, $^{\wedge}p < 0.06$.

Figure 5.

Experiment 3 TMS results at 100 ms after stimulus onset. Current go and nogo trials were collapsed. Following nogoCS+ (compared to nogoCS-) trials, MEPs for CS+ were significantly reduced. MEPs for current CS+ trials were also reduced compared to current CS- trials when the previous trial type was nogoCS+, suggesting a suppressive effect over motor activity. Current CS- trials were unaffected by previous trial type. MEPs are shown normalized by baseline but were log-transformed for statistical analyses due to normality violations. Error bars represent the SEM across participants. $*p < 0.05$

Figure 6.

Experiment 4 TMS results at 500 ms before stimulus onset. Difference scores were computed between the task-relevant FDI (index) muscle and the task-irrelevant ADM (pinky) muscle for previous trial types of nogoCS+ and nogoCS-. The ADM muscle served as a baseline control for non-specific physiological changes. There was significantly reduced FDI activity (relative to ADM) when the previous trial type was nogoCS+ compared to nogoCS-. $*p < 0.05$

Figure 7.

A hypothesized model of the dynamics of response activation and suppression following nogoCS+ and nogoCS- trials. Following nogoCS+ trials (top two boxes), there is selective suppression of the task-relevant effector before the onset of the next trial. If the next trial is a CS+ (upper-left box), the suppressive influence is quickly triggered to prevent CS+ provocation from occurring. If the next trial is a CS- (upper-right box), the suppressive influence is released. Following nogoCS- trials (bottom two boxes), there is quick motor energization for CS+ but not CS- presentation.