UNIVERSITY OF CALIFORNIA, SAN DIEGO

The role of response suppression in controlling motivationally driven action tendencies

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Psychology

by

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2016

The Dissertation of Scott Michael Freeman is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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DEDICATION

To my parents, Steve and Karen Freeman, for their unconditional support, guidance, and advice. Also to my late grandmother, Dvora Freeman, who inspired me to think deeply and to never stop asking questions.

EPIGRAPH

"The true sign of intelligence is not knowledge but imagination"

- Albert Einstein

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ACKNOWLEDGMENTS

I am deeply thankful to many individuals who have contributed to my dissertation, both directly and indirectly. First, I want to thank my advisor, Adam Aron, for his close mentorship and providing me with a clear path towards my dissertation at the outset. Adam greatly contributed to my development as a researcher, a thinker, and a humanitarian. For this, I am extremely grateful. I am also grateful to my dissertation committee for their guidance in preparing my dissertation.

I also want to thank the members of the Aron lab, both past and present. In my first few years as a graduate student, Ian Greenhouse, Adnan Majid, Yu-Chin Chiu, and Jan Wessel were especially helpful in teaching me the methods and tools that I repeatedly used throughout my time at UCSD. I was also fortunate enough to have several phenomenal research assistants throughout my time as a graduate student: Ieva Razhas, Ali Tonnesen, and Dominic Alvernaz.

I want to say a special thanks to a few close friends: Jordan Comins, Sirawaj (Sean) Itthipuripat, and Evan Carr. Thank you Jordan for being a paradigm of modesty and selflessness. Thank you Sean for providing a constant source of comfort, laughter, and support that I will never forget. And thank you Evan for being a best friend in every way possible. Your logical advice, close friendship, contagious motivation to succeed, and comedic relief contributed greatly to my happiness over the past 5 years (note: this includes food challenges).

Finally, I want to thank my family, who has given me unparalleled support and love. It is pretty rare to be able to use your family as a sounding board for your experiments, but then again, my family is pretty rare.

Chapter 1, in full, is a reprint of the material as it appears in *Current Biology*. Freeman, Scott M.; Razhas, Ieva; Aron, Adam R., 2014. The dissertation author was the primary investigator and author of this paper.

Chapter 2, in full, is a reprint of the material as it appears in *Neuropsychologia*. Freeman, Scott M.; Alvernaz, Dominic; Tonnesen, Alexandra; Linderman, David; Aron, Adam, R., 2015. The dissertation author was the primary investigator and author of this paper.

Chapter 3, in full, is currently being prepared for submission for publication of the material. Freeman, Scott M.; Monreal, Teresa; Mello, Melissa; Huh, Paulina, Aron, Adam R.; Boutelle, Kerri, N. The dissertation author was the primary investigator and author of this paper.

Chapter 4, in full, is a reprint of the material as it appears in *Journal of Cognitive Neuroscience*. Freeman, Scott M.; Aron, Adam, R., 2015. The dissertation author was the primary investigator and author of this paper.

Chapter 5, in full, is a reprint of the material as it appears in *Journal of Neuroscience*. Freeman, Scott M.; Itthipuripat, Sirawaj; Aron, Adam, R., 2016. The dissertation author was the primary investigator and author of this paper.

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ABSTRACT OF THE DISSERTATION

The role of response suppression in controlling motivationally driven action tendencies

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The ability to control oneself in the face of temptation is crucial to everyday life. To successfully resist temptation, individuals use many different strategies, including amplifying a long-term goal, focusing attention elsewhere, and suppressing the provoked, inappropriate action tendency. Here, I focus on response suppression, which is highly tractable and has a well-defined neural circuitry. I specifically focus on response suppression in controlling *motivationally driven* action tendencies, which is a crucial element of real-world self-control that has often been ignored. In Chapter 1, I develop a new task that probes if and how response suppression is exerted in the face of a motivationally driven action tendency. Using neurophysiological measures, I show that response suppression plays a key role in controlling such provocations. In Chapter 2, I

find that individuals can also control themselves by suppressing an effector in advance (i.e. proactively), thereby preventing an impending provocation. Then, in Chapter 3, I take advantage of the paradigm we developed in a sample of overweight individuals to examine excessive provocation versus diminished control, which our paradigm is designed to address. I show that individuals with high eating drive are *less* provoked by the motivating stimulus, suggesting that they adopt a safer, more proactive control strategy. In Chapter 4, I elucidate the temporal dynamics of when activation rises and when suppression kicks in. I also show how mental fatigue can diminish individuals' ability to suppress high levels of activation. Finally, in Chapter 5, I examine another type of real-world provocation called motor affordances. I find that affordances depend on the excitatory/inhibitory state of the motor system, which is modulated by cognitive load. This indicates that the motor system can be "set" so that inappropriate provocations do not emerge, which may include motivationally driven provocations. Taken together, the current dissertation shows that both reactive and proactive response suppression play a pivotal role in controlling motivationally driven action tendencies. Importantly, it suggests that the control process relies on many factors, including the strength of the activation, recent "high conflict" exposures, motivational drive, mental fatigue, and the current state of the motor system.

GENERAL INTRODUCTION

Self-control is a crucial component to everyday life. In general, exerting self-control means restraining ourselves from engaging in strongly motivated actions, usually in the service of an overarching goal. A classic, real-world example of self-control is seen in the influential "marshmallow task" (Mischel, Ebbesen, & Zeiss, 1972; Mischel, Shoda, & Rodriguez, 1989), where children resist their immediate temptation to reach out and eat a marshmallow. The ability to resist the temptation in this task has been shown to predict, much later in life, various success measures, including SAT scores, educational attainment, and body mass index (Mischel et al., 1989; Schlam, Wilson, Shoda, Mischel, & Ayduk, 2013; Shoda, Mischel, & Peake, 1990).

Resisting an immediate temptation is not, however, a unitary construct. Rather, it relies on a number of different neurocognitive strategies and mechanisms that work together to help prevent succumbing to temptation. In the marshmallow example, one strategy the child could use to resist temptation is to amplify the goal of not eating the marshmallow. This question of the relative weight or value of a future benefit versus an immediate benefit has been studied using temporal discounting paradigms (Critchfield & Kollins, 2001; Green, Fristoe, & Myerson, 1994; Green, Myerson, & McFadden, 1997; Soman et al., 2005; Story, Vlaev, Seymour, Darzi, & Dolan, 2014). Many such studies have found that overvaluing short-term over long-term goals can lead to self-control failures, including addiction (Anker, Perry, Gliddon, & Carroll, 2009; Housden, O'Sullivan, Joyce, Lees, & Roiser, 2010; MacKillop et al., 2011). Another strategy the child could use is to divert attention away from the provoking marshmallow and onto a

different stimulus. Indeed, redirecting attentional resources can be a powerful form of self-control (Harris, Hare, & Rangel, 2013; Mischel et al., 1972). A third strategy is to cognitively "reappraise" the value of the marshmallow (Gross, 2002). For example, the child could try to imagine that the marshmallow is actually not very tasty or instead focus on the negative health aspects of the marshmallow. This could help reduce the appeal and provocation of the marshmallow, and studies have shown it can be an effective cognitive strategy (Goldin, McRae, Ramel, & Gross, 2008; Hare, Camerer, & Rangel, 2009; Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner & Gross, 2005). Finally, the child could suppress the motor activation that is being provoked by the marshmallow. This means that if the child would normally reach for the marshmallow with the right hand, he or she could suppress the right hand motor activation to help ensure that movement is not made towards the marshmallow. Suppressing motor responses has been observed in a number of studies where a strong action tendency must be withheld (Coxon, Stinear, & Byblow, 2006; Majid, Cai, George, Verbruggen, & Aron, 2012; Stinear, Coxon, & Byblow, 2009).

In this dissertation, I focus on response suppression as a way to control one's actions. A key reason for this focus is because it is perhaps the most experimentally tractable form of self-control for several reasons. First, response suppression tasks can be translated across species, with many core findings consistent across species (Eagle, Bari, & Robbins, 2008). Second, response suppression has a clear and easy to measure behavioral output with reaction times and error rates. And third, the underlying neural mechanisms of response suppression are relatively well delineated and have been shown

to involve a specific network of connected brain regions (Aron, 2007; Bari & Robbins, 2013; Jahanshahi, Obeso, Rothwell, & Obeso, 2015).

Neural circuitry of response suppression

Over the past decade or so, a great deal of evidence has pointed to a network of brain regions involved in reactively suppressing an action (i.e. stopping an action that has been initiated). At the cortical level, this network includes the presupplementary motor area (preSMA) and the right inferior frontal cortex (rIFC) (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Aron, Robbins, & Poldrack, 2014; Nachev, Wydell, O'Neill, Husain, & Kennard, 2007; Swann et al., 2012). One way in which stopping happens is that these cortical regions are thought to communicate with the subthalamic nucleus (STN) of the basal ganglia via a "hyperdirect" pathway to quickly stop or withhold an action tendency (Aron et al., 2007; Schmidt, Leventhal, Mallet, Chen, & Berke, 2013). Neuronal tracing studies have shown that the STN broadly innervates the globus pallidus interna (GPi) (Nauta & Cole, 1978; Smith, Hazrati, & Parent, 1990), thus suppressing thalamocortical drive (Bari & Robbins, 2013; Schmidt et al., 2013). In turn, this broad innervation is hypothesized to have global suppressive effects on the motor system, which has been observed in several studies (Cai, Oldenkamp, & Aron, 2012; Majid et al., 2012; Wessel, Reynoso, & Aron, 2013).

Recent studies have also shown that it is possible to suppress an impending action tendency *before* the action tendency arises (Cai, Oldenkamp, & Aron, 2011; Majid, Cai, Corey-Bloom, & Aron, 2013). Rather than the "hyperdirect" pathway, such proactive suppression is posited to involve the "indirect", striatally-mediated pathway (Majid et al.,

2013; Zandbelt, Bloemendaal, Neggers, Kahn, & Vink, 2013), which may allow more selective, effector-specific suppression (Cai et al., 2011; Greenhouse, Oldenkamp, & Aron, 2012). The conceptual and neural distinction between proactive and reactive suppression highlights the importance of considering what type(s) of response suppression is being recruited in an experimental task (Greenhouse et al., 2012).

Ecological validity of response suppression tasks

The vast majority of studies investigating response suppression use classic tasks from cognitive psychology, including the stop-signal, go/nogo, Simon, and Flanker tasks. These tasks induce prepotent action tendencies by 1) presenting cues that signal a response before it must be stopped (e.g., stop-signal), 2) developing automated tendencies from repeatedly cued actions (e.g., go/nogo), or 3) capitalizing on automatic action tendencies that already exist (e.g., Simon and Flanker) (for review, see Ridderinkhof et al., 2011). In turn, it is thought that requiring people to control such action tendencies provides a basic model for real-world self-control, allowing researchers to better understand when self-control fails. Indeed, several studies have reported that task performance and corresponding brain activations do relate to real-world failures in self-control, including substance abuse (see Smith et al., 2014 for a meta-analysis). For example, individuals affected by substance use disorders have been shown to exhibit longer stop signal reaction times (Ersche et al., 2012; Fillmore & Rush, 2002; Monterosso, Aron, Cordova, Xu, & London, 2005; Whelan et al., 2012)—a measure that reflects the speed of the stopping process. Similar deficits have been found on the go-nogo task in the form of increased nogo errors (Hester & Garavan, 2004; Lane, Moeller,

Steinberg, Buzby, & Kosten, 2007; Verdejo-Garcia, Perales, & Perez-Garcia, 2007). Moreover, even unaffected relatives of substance-dependent individuals display longer stop-signal reaction times, suggesting that impaired response suppression may be a preexisting heritable endophenotype for addictions (Ersche et al., 2012).

Notwithstanding, using these response control tasks as a model for real-world self-control has significant limitations (Aron, 2011). This is evidenced by many studies that have failed to find a relationship between measures of response suppression and self-control failures (e.g., Li et al., 2009; Yan and Li, 2009; Bednarski et al., 2011; Connolly et al., 2012; De Ruiter et al., 2012; Bell et al., 2014). Moreover, the effect sizes in studies that have found such a relationship are often small-to-medium in size (Smith et al., 2014), thus limiting the generalizability of the results.

One reason response suppression tasks are limited as a model of real-world self-control is because response suppression is only one of many different strategies individuals use to control themselves, as previously discussed. Yet, even in the domain of response suppression, the classically used tasks are missing several key elements. One of these is better capturing response suppression that occurs proactively, instead of just reactively. In the marshmallow example, the real world ostensibly requires one to suppress the response to-be-activated by the marshmallow ahead of time (Aron, 2011), or tonically (Aron et al., 2014). Another key element is that real-world response control most often involves controlling an action tendency, or provocation, that is driven by a strong motivational desire for reward. Such provocations include foods, drinks, money, drugs, and sex, which are usually driven by dopaminergic bursts in the mesolimbic pathway of the brain (Berridge, 2007; Everitt & Robbins, 2005; Li et al., 2015; Wassum,

Ostlund, Loewinger, & Maidment, 2013). In this dissertation, I look to expand the current literature by focusing on the role of reactive and proactive response suppression in controlling motivationally driven provocations.

Techniques to study response suppression

While many different techniques have been used in humans to study response suppression—including functional neuroimaging (Aron & Poldrack, 2006; Jahfari, Stinear, Claffey, Verbruggen, & Aron, 2010), intracranial and extracranial electroencephalography (Schevernels et al., 2015; Swann et al., 2009, 2011), deep brain stimulation (Ray et al., 2012; Swann et al., 2011; Witt et al., 2004), and transcranial magnetic stimulation (TMS) (Coxon et al., 2006; Greenhouse, Oldenkamp, & Aron, 2012; Leocani, Cohen, Wassermann, Ikoma, & Hallett, 2000; van den Wildenberg et al., 2010)—in this dissertation, I primarily rely on the TMS technique. This is because TMS (along with concurrent electromyography, or EMG) measures motor excitability of a particular muscle representation (e.g., the right index finger) and reflects cortical, subcortical, and spinal influences. As a result, stronger claims can be made about response activation and suppression. Another reason I rely on TMS is that it provides excellent temporal resolution on the order of milliseconds. This level of resolution is highly beneficial when trying to distinguish one neurocognitive process from another (e.g. response activation generated by a rewarding stimulus versus suppression of that response, which could occur within 100 milliseconds or less).

Dissertation aims

This dissertation addresses the role of response suppression in mitigating motivationally driven action tendencies. Under this overarching theme, there are six specific aims: 1) to develop a new paradigm that requires participants to control a motivationally driven action tendency, 2) examine if, when, and how response suppression is part of such control, 3) investigate if response suppression has any downstream effects on provocation (e.g., can reduce the future impact of provocations), 4) explore response activation and suppression in a sample of overweight individuals, 5) elucidate the motor dynamics of both the activation and suppression processes, and 6) extend the investigation of response suppression to another type of real-world provocation.

I begin in Chapter 1 by developing a new response control task that was designed to examine how people exert response suppression in the face of a motivating stimulus (*Aim 1*). On each trial, thirsty participants had to press a button multiple times to earn a juice reward. Sometimes the stimulus "energized" their pressing, because it has been earlier associated with juice through Pavlovian learning. The key behavioral condition of interest was when the motivating, Pavlovian stimulus energized pressing but the participant was required to withhold the press. I expected that this setup more accurately mimics the real world requirement to suppress a response when the action is motivationally driven. With this paradigm, I test the following questions: a) When pressing is allowed, does the motivating stimulus rapidly generate an action tendency, and b) When pressing is not allowed, does response suppression "kick in" to mitigate the provocation (*Aim 2*)?

In Chapter 2, I test if suppressing a motivationally driven action tendency has any downstream effects on future provocation. I was particularly interested in the possibility that suppressing motivational provocations more often can actually reduce the future impact of those provocations (*Aim 3*). To test this, three independent groups of participants were exposed to different proportions of trials where they had to withhold action in the face of a motivating (versus non-motivating) stimulus. I then examined how much the motivating stimulus provoked them on trials in which they were allowed to press, and if the amount of provocation was different across the three groups.

While Chapters 1 and 2 provide a foundation for the role of response suppression in controlling motivationally driven action tendencies, it is unclear how the provocation and control differ across individuals. Thus, Chapter 3 expands on Chapters 1 and 2 by testing the same paradigm in a sample of mostly overweight individuals with varying levels of reward eating drive (*Aim 4*). To increase motivational levels in this population, we used highly caloric chocolate- and vanilla-flavored milk instead of juice. We then investigated potential group differences in sensitivity to the motivating stimulus, both on trials when they were allowed to press and on trials when they were not.

In Chapter 4, I shift the focus to the activation-suppression dynamics that are suggested by the results in Chapter 1. This is important because understanding how quickly the activation occurs, when the suppression "kicks in", and how these two processes are related to one another can inform what process goes awry when individuals struggle to control their actions. To map the dynamics, TMS pulses are needed at several different time points following the stimulus onset. Because there can only be one TMS pulse per trial, we needed to substantially increase the number of trials in the experiment.

Unfortunately, trial numbers are restricted in the paradigm used in Chapters 1-3 due to eventual satiation of the liquid reward and limited Pavlovian learning; thus, we modified the task to use monetary rewards instead. Now, we sought to reveal the finer-grained dynamics of the predicted motor activation and motor suppression processes—how fast the activation appears, how high it reaches, when the control kicks in, how long it lasts, and if the suppression process relates to the strength of the preceding activation (*Aim 5*). Finally, to investigate why people sometimes fail to control their actions, we examined if and how the activation-suppression dynamics relate to how successful participants are in withholding their reward-driven actions.

Finally, in Chapter 5, I look to extend my research on control over motivational provocations to a different type of real-world provocation, called motor affordances (*Aim 6*). These occur when the visual properties of an object elicit behaviorally relevant motor representations (e.g., viewing a right-facing cup handle activates left hemisphere motor, resulting in potentiation of the right hand). We investigated the idea the frontal cortex helps ensure that irrelevant affordance provocations remain below the threshold for actual movement. We also examined how the presence (or absence) of affordances relates to the excitatory/inhibitory state of the motor system. This information could help elucidate how the brain deals with and ostensibly controls irrelevant provocations, including those that are motivationally driven.

Table 0.1: Summary of Chapters

Chapter	Task Used	Methods Used	Aims Addressed
1	Go-nogo/PIT	Behavior and TMS	(*1*) Develop new paradigm (*2*) Examine role of response suppression
2	Go-nogo/PIT	Behavior and TMS	(*3*) Investigate downstream effects of response suppression
3	Go-nogo/PIT	Behavior	(*4*) Explore response activation and suppression in a sample of overweight individuals
4	Rewarded go-nogo	Behavior and TMS	(*5*) Elucidate activation-suppression dynamics
5	Motor Affordance/WM	EEG	(*6*) Extend to a different type of real-world provocation

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CHAPTER 1

Top-down response suppression mitigates action tendencies triggered by a motivating stimulus

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As it appears in

Current Biology

2014

Volume 24, Issue 2, Pages 212-216

Current Biology 24, 212–216, January 20, 2014 ©2014 Elsevier Ltd All rights reserved http://dx.doi.org/10.1016/j.cub.2013.12.019

Report

Top-Down Response Suppression Mitigates Action Tendencies Triggered by a Motivating Stimulus

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Summary

Motivating stimuli provoke action tendencies that sometimes lead to unwanted behavior (e.g., eating chocolate when trying to diet) [1–4]. Implementing control over these provocations is essential to healthy functioning [1, 5]; however, few laboratory-based models of such control exist. Here we developed a novel task in which thirsty human subjects made instrumental responses to obtain a juice reward (Go trials) or were required to withhold responding (NoGo trials) in the presence of a rewarded (CS+) or unrewarded (CS−) conditioned stimulus. For Go trials, single-pulse transcranial magnetic stimulation revealed a rapid increase in motor activity for CS+ versus CS−, preceding more vigorous instrumental responding. Critically, successful NoGo trials resulted in suppression of motor activity for CS+, but not CS−. Moreover, while there was broad excitation in the hand muscles in Go trials, suppression in NoGo trials was selective to the effector that could obtain reward. These results show that response suppression can be triggered by a motivational stimulus, thus providing a richer model of self-control than classic cognitive psychology paradigms.

Results

We often encounter motivating stimuli that prompt action tendencies that conflict with our long-term goals, requiring self-control [1, 6–8]. While such self-control can be achieved using high-level strategies such as reappraisal and distraction [9–11], here we tested the hypothesis that it can also be achieved by suppressing action tendencies triggered by the motivating stimulus.

We developed a novel paradigm that combined Pavlovian-to-instrumental transfer (PIT)—an associative learning phenomenon in which a conditioned stimulus motivates instrumental behavior [12]—with a Go/NoGo task. As in classic PIT experiments [13–15], there were three phases (Figure 1A). In the instrumental phase, thirsty subjects learned to press a button with their right index finger to get juice in Go trials and to withhold responding in NoGo trials. In the Pavlovian phase, they learned which color (green or purple) predicted juice delivery (i.e., CS+ or CS−). In the transfer phase, in Go trials, they again pressed to get juice, but now with a motivating (CS+) or nonmotivating (CS−) stimulus in the background; in NoGo trials, responding was to be withheld in the presence of CS+ or CS−. We specifically asked two questions: (1) In Go trials, does the motivating stimulus (CS+) rapidly generate an action tendency? (2) In NoGo trials, does the presence of a NoGo control goal mitigate the action tendency by recruiting response suppression?

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Experiment 1

To address these questions, we measured PIT behavior and "imaged" the motor system using single-pulse transcranial magnetic stimulation (TMS). TMS was applied over left motor cortex while electromyography was measured from the right hand. This measures corticospinal excitability (CSE) of the hand representation, reflecting cortical, subcortical, and spinal influences.

In the Pavlovian phase, subjects made speeded responses according to the location of a colored rectangle for the CS+ and CS− stimuli [16] (Figure 1A). The CS+ color always predicted juice delivery, while the CS− color always predicted no juice delivery. Subjects were told that juice delivery during this phase had no relationship to the button press (which was done with the left hand; see Figure 1A). Data were analyzed from 14 subjects. An ANOVA with the factors of Stimulus (CS+/CS−) × Time (first half of phase/second half of phase) revealed a significant main effect of Stimulus ($F_{1,13} = 6.5$, $p = 0.02$), with response time (RT) faster for CS+ than CS−, and a significant Stimulus × Time interaction ($F_{1,13} = 8.6$, $p = 0.01$). T tests showed that the difference in RT for CS+ versus CS− emerged most strongly during the second half of the Pavlovian phase (first half: $p = 0.3$; second half: $p = 0.002$) (see Figure S2 available online). Thus, although juice delivery was independent of responding, subjects responded more quickly to the CS+ than the CS− stimulus across time, providing evidence for learning of reward values.

To examine PIT behavior, we analyzed the first and the second halves of the transfer phase separately (first half: blocks 1 and 2; second half: blocks 3 and 4). We predicted stronger PIT for blocks 1 and 2 based on a pilot experiment in which the PIT effect waned in the transfer phase (Table S1), probably because (1) Pavlovian learning was short (~7 min) and (2) the Pavlovian background cue was functionally irrelevant in the transfer phase, leading to reduced processing of the cue over time. Note that a real-world Pavlovian stimulus could be reinforced for years; here we simply focus on the time period when the association was still strong (i.e., in blocks 1 and 2) as a model of control over a motivating stimulus. We compared CS+ and CS− with three different behavioral measures: (1) mean number of presses in Go trials, (2) mean first-press RT in Go trials, and (3) percentage of errors in NoGo trials. Paired t tests showed that, across all three behavioral measures, PIT was present in blocks 1 and 2 (all p values: $p < 0.05$) but not blocks 3 and 4 (all p values: $p > 0.2$) of the transfer phase (Figures 2A–2C). The PIT effects of first-press RT and number of presses indicate that the CS+ invigorated instrumental responding in Go trials. Moreover, the increased errors in NoGo CS+ trials suggest that the CS+ provoked an action tendency even in NoGo trials.

In each trial, a TMS pulse was delivered 250 ms after stimulus onset to measure CSE (Figures 1B and 1C). CSE was simultaneously recorded from the first dorsal interosseous (FDI) muscle of the right index (task-relevant) finger and the abductor digiti minimi (ADM) muscle of the right pinky (task-irrelevant) finger. TMS was delivered in Go and NoGo trials for CS+ and CS−, and also for Null trials to provide a baseline (see Figure 1B). Mean CSE for each condition

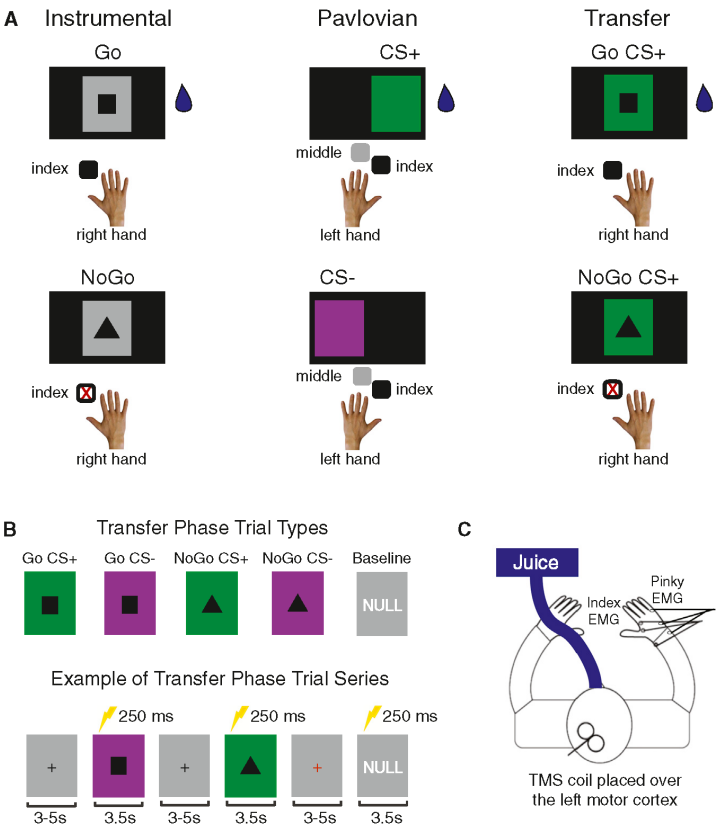

Figure 1. Task Design

(A) Three phases. In the instrumental phase, subjects continuously pressed with the right index finger to obtain juice in Go (square) trials. Juice delivery was based on a variable ratio reward schedule (5–15 presses, mean = 10). In NoGo (triangle) trials, no press was to be made; otherwise, an error message was displayed (not shown). In the Pavlovian phase, subjects 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) and was never delivered for the CS− color (shown as purple). The transfer phase was identical to the instrumental phase, except that the Pavlovian colors (rather than gray) appeared in the background. In the transfer phase, in Go trials, juice was delivered to maximize motivation (this is different from typical PIT paradigms that are done in extinction). In NoGo trials, no juice was delivered, thus resembling the outcome of successful withholding in the real world. Thirst level and pleasantness ratings remained high throughout the experiment (see Figure S1).

(B) Trial types and example trial series for transfer phase. For baseline trials, a red fixation cross informed the subject that the following trial would display "NULL" and the subject was to rest during this time. TMS pulses were delivered 250 ms after stimulus onset.

(C) Experimental setup. TMS was applied over the left primary motor cortex. Electromyography was recorded simultaneously from the index and pinky fingers of the right hand. See also Supplemental Experimental Procedures.

was normalized by dividing by this baseline (i.e., a value of 1 represents no change). Because PIT was only present during blocks 1 and 2 of the transfer phase (Figures 2A–2C), the CSE results presented below reflect these blocks only (see Figure S3 for CSE results from blocks 3 and 4 of the transfer phase).

For the FDI muscle, an ANOVA performed on CSE for the factors of Stimulus (CS+/CS−) × Cue (Go/NoGo) revealed a significant main effect of Cue ($F_{1,13} = 8.17$, $p = 0.01$) and a significant Stimulus × Cue interaction ($F_{1,13} = 5.37$, $p = 0.04$). For Go trials, CS+ had significantly higher CSE than both CS− and baseline ($p < 0.05$) (Figure 2D). This attests to a quick response activation elicited by the CS+. Importantly, there was a reduction of CSE in NoGo trials for CS+ ($t_{13} = 2.35$, $p = 0.035$), but not for CS− ($t < 1$, not significant) (Figure 2D). This suggests that response suppression was used to countermand the motivating influence of CS+ when a response was successfully withheld.

To better quantify the degree of CSE reduction from Go to NoGo, we calculated the percent change for CS+ and CS− (e.g., for CS+ trials: (NoGo CS^+ − Go CS^+) × (100/Go CS^+)). Whereas CS− showed only a 2% reduction in CSE from Go to NoGo trials, CS+ showed an 18% reduction. The change for CS+ was significantly higher than for CS− ($t_{13} = 2.28$, $p = 0.04$) and was significantly below a no-change value of 0 ($t_{13} = 3.73$, $p = 0.003$) (Figure 2E).

We examined the selectivity of the motor excitation and suppression by comparing CSE for the task-relevant FDI muscle and the task-irrelevant ADM muscle. Because the data were nonnormally distributed (Shapiro-Wilk W test: $p < 0.001$) (due to high variability in ADM), we log-transformed the normalized CSE and performed an ANOVA for Muscle (FDI/ADM) × Cue (Go/NoGo) × Stimulus (CS+/CS−). There was a significant main effect of Cue ($F_{1,13} = 9.42$, $p = 0.009$) and a significant Muscle × Cue × Stimulus interaction ($F_{1,13} = 4.76$, $p = 0.048$).

Follow-up ANOVAs were performed for FDI and ADM muscles separately. Whereas the FDI showed a significant Cue × Stimulus interaction (as presented above), the ADM showed a marginally significant main effect of Stimulus—i.e., CSE was higher for CS+ than CS− ($F_{1,13} = 4.18$, $p = 0.06$) (Figure 2F; figure depicts nontransformed values). Thus, for ADM, CSE was increased for CS+ versus CS− overall. For FDI, CSE was increased for CS+ in the Go condition but suppressed in the NoGo condition. This suggests that, for CS+ trials, the motor excitation was broad across the hand, while motor suppression during NoGo trials was restricted to the task-relevant index finger. This pattern was further confirmed using an ANOVA for Muscle (FDI/ADM) × Stimulus (CS+/CS−) in NoGo trials alone. There was a significant interaction ($F_{1,13} = 10.23$, $p = 0.007$) in which CSE for CS+ (compared to CS−) was reduced in the FDI muscle but significantly increased in the ADM muscle (post hoc paired t test: $t_{13} = 2.47$, $p = 0.03$). In addition to providing evidence for selective suppression, increased CSE for NoGo CS+ in the ADM muscle argues

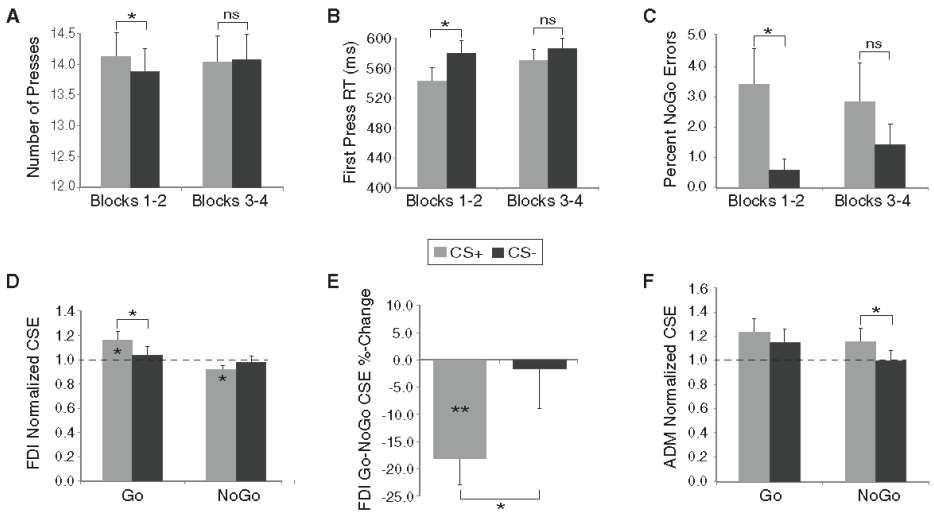

Figure 2. PIT Behavior and CSE Results

(A) Mean number of presses to obtain juice was significantly higher for CS+ than CS− during blocks 1 and 2.

(B) Mean first-press RT was significantly faster for CS+ than CS− during blocks 1 and 2.

(C) Percentage of NoGo errors was significantly higher for CS+ than CS− during blocks 1 and 2. See also Figure S2 for Pavlovian phase results and Table S1 for behavioral results from pilot experiment.

(D) Normalized CSE for FDI (task-relevant) muscle in blocks 1 and 2. A value of 1 represents the same CSE as baseline (Null). For Go trials, CSE for CS+ was higher than both CS− and baseline. For correct NoGo trials, CS+ was reduced below baseline, leading to a significant interaction. See also Figure S3 for CSE results from blocks 3 and 4 and Table S2 for FDI raw CSE values.

(E) For FDI muscle in blocks 1 and 2, values represent percent change from Go trials to NoGo trials for CS+ and CS−.

(F) Normalized CSE for ADM (task-irrelevant) muscle in blocks 1 and 2. CSE is shown normalized by baseline but was log-transformed for statistical analyses due to normality violations. The ADM muscle shows a general CSE increase for CS+. Error bars represent the SEM across subjects. **$p < 0.01$, *$p < 0.05$.

against the possibility that the observed suppression is due to higher-level processes that downmodulate action values because such an interpretation would predict similar patterns of excitation across the hand.

Experiment 2

The foregoing demonstrates a PIT effect in the transfer period: in Go trials, responding was energized for CS+ versus CS−. If this depends on motivational state, then it should dissipate with a satiation manipulation that devalues the juice reward [17–20]. Thus, we repeated the behavioral procedure from experiment 1, but in both Satiation (n = 20) and No Satiation (n = 20) groups. Subjects in the Satiation group were given 4 min between the Pavlovian and transfer phases to consume juice until they were no longer thirsty, while subjects in the No Satiation group were instructed to simply wait quietly during the 4 min.

An ANOVA was performed using Drive (Satiation/No Satiation) as a between-subjects factor and Stimulus (CS+/CS−) as a within-subjects factor. For number of presses (Go trials), there was a main effect of Drive ($F_{1,38} = 7.46$, $p < 0.01$) and a significant Stimulus × Drive interaction ($F_{1,38} = 4.94$, $p = 0.03$). There was a significant increase in number of presses for CS+ versus CS− for the No Satiation group ($t_{19} = 2.27$, $p = 0.03$), replicating experiment 1, but not for the Satiation group ($t_{19} = 1.81$, p = not significant) (Figure 3A). For first-press RT (Go trials) and percentage of NoGo errors (NoGo trials), there were no significant main effects or interactions. However, for first-press RT, there was a marginally significant difference between CS+ and CS− in the No Satiation group ($t_{19} = 1.8$, $p = 0.09$), while the Satiation group showed no difference ($t < 1$) (Figure 3B). The percentage of NoGo errors was also higher for CS+ versus CS− in the No Satiation group ($t_{19} = 2.34$, $p = 0.03$), replicating experiment 1, while there was no difference in the Satiation group ($t_{19} = 1.14$, p = not significant) (Figure 3C).

Discussion

We asked whether response suppression is used to withhold an action that is provoked by a motivating stimulus. Behaviorally, we show that thirsty subjects are indeed provoked by a reward-predicting (CS+) stimulus, evident in invigorated instrumental responding during the transfer phase. Consistent with this, the influence of CS+ was also present in NoGo trials, as evidenced by increased NoGo errors compared to CS− trials. In experiment 2, we replicated these results in the No Satiation group, and we also showed that the PIT effects disappeared with satiation, confirming a dependence on basic motivational drive. The TMS results corroborated these findings and showed that in Go trials, there was an early increase in CSE (at 250 ms) for CS+ compared to CS− and also compared to baseline. Importantly, in NoGo trials, TMS showed that CSE was reduced beneath baseline for CS+ (but not CS−), indicating suppression over the action tendency generated by the CS+. Furthermore, the analysis of the two fingers of the right hand showed that while the motivating influence of CS+ affected

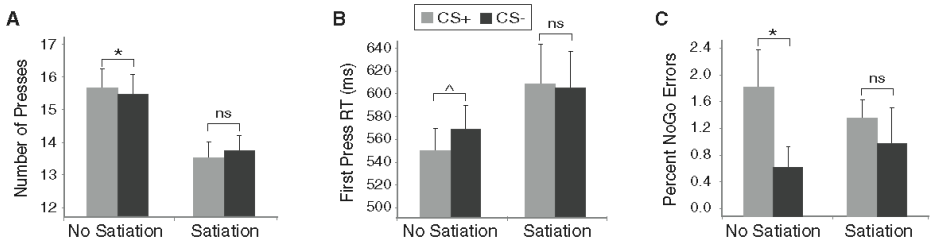

Figure 3. Transfer Phase Results from Experiment 2

(A) Average number of presses to obtain juice was significantly higher for CS+ than CS− in the No Satiation group, but not in the Satiation group (and there was an interaction).

(B) First-press RT was marginally significantly faster for CS+ than CS− in the No Satiation group, but not in the Satiation group.

(C) Percentage of NoGo errors was significantly higher for CS+ than CS− in the No Satiation group, but not in the Satiation group. Error bars represent the SEM across subjects. *$p < 0.05$, ^$p < 0.1$. All statistical tests for experiment 2 were one-tailed due to its replicative nature. See Supplemental Experimental Procedures.

both fingers (presumably global for the hand and perhaps also the wider motor system), the suppression exerted in NoGo CS+ trials was selective to the task-relevant index finger.

Taken together, these results show that one way humans exert control over Pavlovian-induced action tendencies [6, 7] is by directing response suppression over the provoked action. This is likely a different form of response suppression than is captured by standard paradigms such as stop signal and Go/NoGo (e.g., [21]). In those paradigms, there is strong response prepotency, and the response suppression is triggered by an external stimulus. However, there was little general prepotency here (because Go and NoGo trials occurred with equal probability, mean RT was a slow 560 ms, and Go CS− trials showed no CSE increase). Furthermore, control was not merely triggered here by an external stimulus but, instead, most likely by the conflict between the response activation and the NoGo rule on CS+ trials. In that sense, there is some commonality with tests of response conflict such as the Simon and antisaccade tasks [22, 23]. Yet what distinguishes our paradigm from these is that, in this study, the response activation is driven by the motivation-action spillover of the conditioned stimulus rather than by automatic stimulus-response links. This is clear in that response suppression only occurred for CS+ trials and, as experiment 2 shows, only when the subjects were thirsty.

We also observed that response suppression was targeted at the task-relevant finger, rather than the global hand. Based on recent results for selective response suppression, this predicts a frontal-striatal involvement in the current task [24]. Future studies could test this, as well as the possibility that control targets the ventral striatum/accumbens [25, 26], perhaps via a different fronto-striatal system [27–29]. An alternative explanation for the selective suppression finding is that, in NoGo trials, suppression of the FDI muscle was a result of "surround inhibition" of the activated ADM [30]. However, "surround inhibition" has only been demonstrated when the task-relevant muscle is activated, which was not the case here. Furthermore, there was an increase of CSE for Go CS+ trials across both FDI and ADM muscles (not an ADM increase and an FDI suppression, as surround inhibition would predict).

Taken together, our results suggest a dynamic model of response activation and suppression triggered by the CS+ stimulus (Figure 4). We propose that, in successful NoGo trials, an early activation is generated by the CS+, which conflicts with the NoGo rule. This conflict then triggers response suppression over the action tendency in order to withhold responding. This predicts that, in unsuccessful NoGo CS+ trials, there would be higher CSE (i.e., no suppression)—a prediction that can be tested in a future experiment that generates a larger number of NoGo errors. By contrast, in NoGo CS− trials, we propose that no response suppression was required due to equiprobable Go/NoGo trials (little prepotency) and a nonmotivating CS− stimulus, which erodes the need for response suppression. Future experiments could directly test the proposed dynamics of this activation-suppression model by using more TMS time points or a high-resolution temporal measure such as electroencephalography.

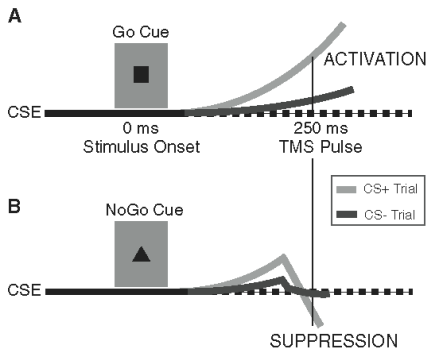

Figure 4. A Model of the Presumed Temporal Dynamics of Response Activation and Suppression in Go and NoGo Trials

(A) In Go trials, CSE increases sooner and at a steeper slope for CS+ compared to CS−. This results in higher levels of CSE for CS+ versus CS− when the TMS pulse is applied 250 ms after stimulus onset, as well as more invigorated behavioral responding.

(B) In correct NoGo trials, CSE begins to increase sooner and at a steeper slope for CS+ than CS− (similar to Go trials). However, by 250 ms after stimulus onset, strong response suppression is implemented over the response activation elicited by CS+ to avoid responding. For CS− trials, response suppression is unnecessary due to lesser response activation from the CS− stimulus.

Supplemental Information

Supplemental Information includes Supplemental Experimental Procedures, three figures, and two tables and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2013.12.019.

Acknowledgments

We thank Charlotte Prevost and John O'Doherty for helpful comments on task design, Jordan Comins and Mary Smith for comments on the manuscript, and the National Institutes of Health for funding (grant DA026452).

Received: September 5, 2013
Revised: October 24, 2013
Accepted: December 10, 2013
Published: January 9, 2014

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Chapter 1, in full, is a reprint of the material as it appears in *Current Biology*. Freeman, Scott M.; Razhas, Ieva; Aron, Adam R., 2014. The dissertation author was the primary investigator and author of this paper.

Supplemental Information

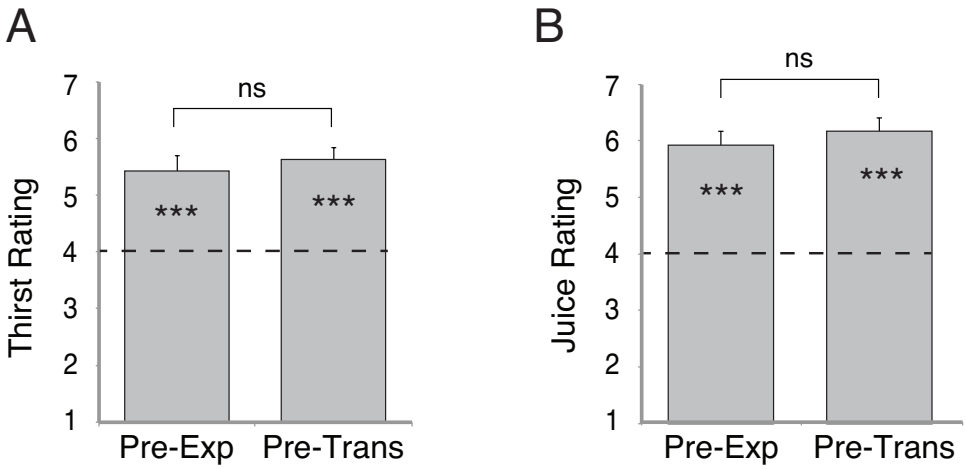

Figure S1.1: Related to Figure 1. (A) Mean thirst ratings taken before the experiment began and immediately before the transfer phase (1=Not at all thirsty; 4=Somewhat thirsty; 7=Extremely thirsty). Ratings showed subjects' thirst levels were significantly above a 'neutral' rating of 4. Thirst levels did not decrease across time, indicating equal motivation across all phases. (B) Mean ratings of how much subjects liked the juice they chose for the experiment (1=Not at all; 4=Somewhat; 7=A lot). Ratings showed subjects enjoyed the juice significantly above a 'neutral' rating of 4. Similar to thirst levels, juice ratings did not decrease across time. Error bars represent the SEM across subjects. ***$p < 0.001$.

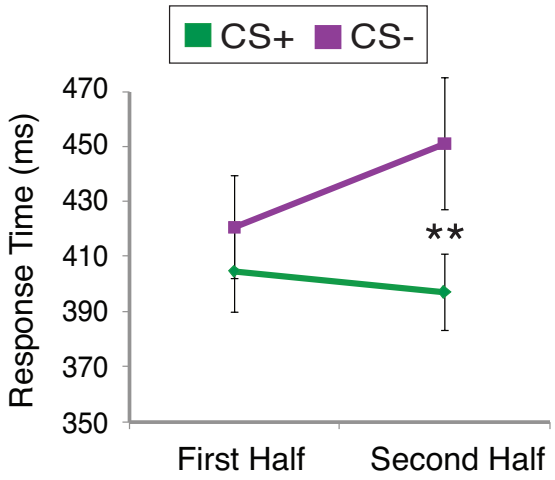

Figure S1.2: Related to Figure 2A-C. Pavlovian phase behavioral results. An ANOVA was performed on RTs with the factors of Stimulus (CS+/CS-) x Time (first half of phase/second half of phase). There was a significant main effect of Stimulus ($F_{1,13} = 6.5$, $p = 0.02$), with RT faster for CS+ than CS-, and a significant Stimulus x Time interaction ($F_{1,13} = 8.6$, $p = 0.01$). Follow-up *t*-tests showed that the difference in RT for CS+ vs. CS- emerged most strongly during the second half of the Pavlovian phase (first half: $p = 0.3$; second half: $p = 0.002$). Thus, although juice delivery was independent of responding, subjects responded more quickly to the CS+ than the CS- stimulus across time, providing evidence for learning of reward values.

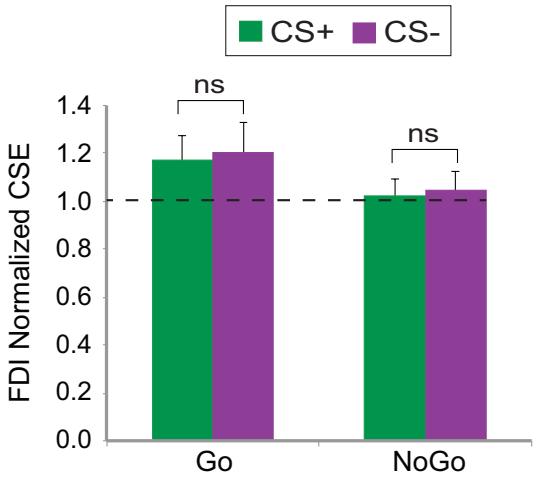

Figure S1.3: Related to Figure 2D-F. For blocks 3-4, there was a marginally significant main effect of Cue, $F_{1,13} = 4.59$, $p = 0.052$, with go trials showing more motor activation than nogo trials. Congruent with the behavioral results from blocks 3-4 that showed no PIT effect, there was no CSE difference between CS+ and CS- during blocks 3-4 for go and nogo trials.

Table S1.1: Related to Figure 2A-C. *P*-values and effect sizes for first half and second half of the transfer phase from a pilot experiment. For first press RT and percentage of nogo errors, the PIT effect size (CS+ vs. CS-) reduced during the second half, suggesting that the PIT effect may dissipate across time.

	1st Half	**2nd Half**
First Press RT		
P-value	0.05	0.15
Cohen's D	0.58	0.43
Number of Presses		
P-value	0.22	0.21
Cohen's D	0.36	0.36
Percent nogo Errors		
P-value	0.17	0.27
Cohen's D	0.39	0.31

Table S1.2: Related to Figure 2D. Raw CSE values (in mV) for the TMS data in Experiment 1. Values inside parentheses represent standard deviation.

	FDI	**ADM**
goCS+	0.72 (0.18)	0.33 (0.19)
goCS-	0.64 (0.18)	0.31 (0.21)
nogoCS+	0.59 (0.18)	0.32 (0.22)
nogoCS-	0.62 (0.17)	0.28 (0.22)
Null	0.65 (0.22)	0.30 (0.20)

Supplemental Experimental Procedures

EXPERIMENT 1

Participants

Seventeen subjects (eleven female) participated (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 [MEPs reflect corticospinal excitability, CSE]. Thus, all analyses for Experiment 1 were run on 14 subjects. All subjects provided IRB consent and passed TMS safety screening.

Task Description

The subjects were instructed to abstain from drinking for a minimum of three hours before arrival. Upon arrival they selected one of four possible juice types (peach Snapple, apple juice, orange juice, and fruit punch). Thirst level and pleasantness of juice were rated before the experiment and before the transfer phase.

Instrumental Phase

Subjects were presented with a large gray rectangle on a black background. In the center there was a black triangle, a black square, or white text that read, “NULL”, for 3.5 s (Figure 1). A square trial denoted go; i.e. the subject could continuously press a button with the right index finger to obtain a drop of juice (0.5 ml). Juice was delivered on a variable ratio reward schedule (5-15 presses; 10 on average) and the number of presses needed on a given trial was randomly generated and pre-determined (i.e., assigned before the experiment began) for each subject. Information regarding the number of presses for juice delivery was not disclosed to the subject. 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 3.5 s trial. This circle allowed subjects to gain a general understanding of how many presses were needed for juice delivery. A triangle trial denoted nogo: i.e., if a press was made, 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. If the fixation cross was red (as opposed to black), it indicated that the following trial would be a Null trial and to simply rest on those trials. Square (go), triangle (nogo), and baseline (Null) trials occurred with equal probability (1/3). All trials were presented pseudo-randomly and there were 24 total trials (8 per condition). All subjects engaged in a practice instrumental session of 12 trials (4 per condition).

Pavlovian Phase

A large purple or green rectangle appeared on either the left or right side of the computer screen with a black background. If the rectangle appeared on the left side of the screen, subjects pressed with the middle finger of their left hand as fast as possible. If the rectangle appeared on the right side of the screen, subjects pressed with the index finger of their left hand 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 counterbalanced across subjects. For CS+ trials, juice was always delivered 1.5 s after stimulus onset and the rectangle remained on the screen for an additional 2 s for a total trial duration of 3.5 s. Subjects 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).

Transfer Phase

The transfer phase was identical to the instrumental phase, with three exceptions. First, there was no longer a black circle to indicate impending juice delivery. This encouraged subjects to keep pressing throughout the trial because they did not know if juice would be delivered, allowing us to measure the number of presses. Second, the

background color was green or purple (CS+ or CS-) for go and nogo trials; but it was gray on baseline trials (Figure 1b). Third, the transfer phase had four blocks, each consisting of 50 trials (10 goCS+, 10 goCS-, 10 nogoCS+, 10 nogoCS-, 10 baseline), yielding 200 total trials (40 per condition).

Juice Delivery

Juice was delivered by an NE-500 OEM syringe pump (New Era Pump Systems, Inc., NY). A syringe was filled with the juice selected by the subject. For each rewarded trial, the pump delivered 0.5 mL of liquid to the subject's mouth via a ~1.5 m long polyethylene plastic tube. The tube rested in the subject's mouth throughout the experiment.

Transcranial Magnetic Stimulation

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 and the abductor digiti minimi 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 [1]. 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 subject was performing the task in a practice session. This was the intensity used during the experiment proper. For every trial, a TMS pulse was delivered 250 ms after the onset of the stimulus. We chose to stimulate at 250 ms because response suppression typically occurs ~150 ms after an explicit signal [2-4], and because in the current paradigm, response suppression is not triggered by the nogo cue (as there are equal proportions of go/nogo trials), but probably

by the detection of the response activation arising from the CS+. We thus added the time likely needed for CS+ visual processing and response activation (~100 ms) to the 150 ms likely needed for response suppression, yielding a total of 250 ms.

Behavioral Analysis

Pavlovian Phase

RTs were recorded for each of the 60 trials (30 CS+, 30 CS-). All incorrect trials and trials in which the RT was greater than three standard deviations from the condition mean were excluded from analysis. Mean RTs were calculated for the first and second half of the Pavlovian phase separately to investigate learning across time.

Transfer Phase

RTs were recorded for each of the 80 go trials (40 CS+, 40 CS-) and errors of commission were recorded for nogo trials. Transfer phase results were analyzed separately for the first half (blocks 1 and 2) and the second half (blocks 3 and 4).

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 0.05 mV or if the amplitude maxed out at 2 mV. Mean peak-to-peak amplitudes of MEPs were calculated for all conditions. To minimize outliers, all values more than three standard deviations away from the condition mean were removed. Errors of commission on nogo trials were excluded from analysis. An auxiliary analysis examined root mean square EMG for the 100 ms time window before the TMS pulse. An ANOVA showed no significant main effects or interactions (all Ps > 0.6), demonstrating that the results are not contaminated by differences in the pre-TMS period.

EXPERIMENT 2

Participants

Forty subjects (thirty-four female) participated (mean age = 20.5, SD = 1.6). All provided IRB consent.

Task Description

The task procedure in Experiment 2 was identical to Experiment 1, with the following exceptions. First, there were now two groups: Satiation and No Satiation. Second, both groups had a four-minute delay period between the Pavlovian and transfer phases; however, in the Satiation group, subjects consumed the juice until they were either a 1 or 2 on thirst level out of a possible 7 (1 – Not thirsty at all; 4- Somewhat thirsty; 7 – Extremely thirsty). In contrast, subjects in the No Satiation group were given pretzels until they were a 6 or 7 on thirst level. Due to the four-minute delay between the Pavlovian and transfer phases, we predicted slightly weaker effects for the No Satiation group in Experiment 2 compared to blocks 1-2 in Experiment 1—a prediction we found to be true (see Results). Third, since the purely behavioral dependent measures in Experiment 2 did not require a baseline reference point, Null baseline trials were no longer included. Fourth, the symbols used for go and nogo trials (square and triangle) were counterbalanced across subjects in addition to the CS counterbalancing. Fifth, the transfer phase for Experiment 2 consisted of three blocks with 40 trials in each block (120 total trials). We confirmed the effectiveness of the satiation manipulation via self-report measures of thirst level and subjects' desire for the juice, which revealed significantly lower scores in the Satiation group on both measures (Ps < 0.001). There were no between-group differences in age or gender: Ps > 0.35.

Supplemental References

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CHAPTER 2

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

Freeman, S.M., Alvernaz, D., Tonnesen, A., Linderman, D., and Aron, A.R.

As it appears in

Neuropsychologia

2015

Volume 68, Pages 218-231

Neuropsychologia 68 (2015) 218–231

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

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

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ARTICLE INFO

Article history:
Received 1 October 2014
Received in revised form
16 December 2014
Accepted 11 January 2015
Available online 13 January 2015

Keywords:
Cognitive control
Motivation
Conflict adaptation
Pavlovian-to-instrumental transfer
Transcranial magnetic stimulation

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 et al., 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.

1. Introduction

The environment is filled with reward-predicting, Pavlovian stimuli that can motivate our actions (Cavanagh et al., 2013; Gupta and Aron, 2011; Hajcak et al., 2007; Talmi et al., 2008) and bias our decisions (Bray et al., 2008; Chiu et al., 2014; Klein-Flügge and 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 et al., 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 behavior[1] (Holmes et al., 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

[1] The 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.

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http://dx.doi.org/10.1016/j.neuropsychologia.2015.01.016
0028-3932/

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 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 et al., 2011; Duque et al., 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 and related paradigms, where 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 et al., 2005; Ferrey et al., 2012; Houben and Jansen, 2011; Kiss et al., 2008; Wessel et al., 2014). 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 et al., 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

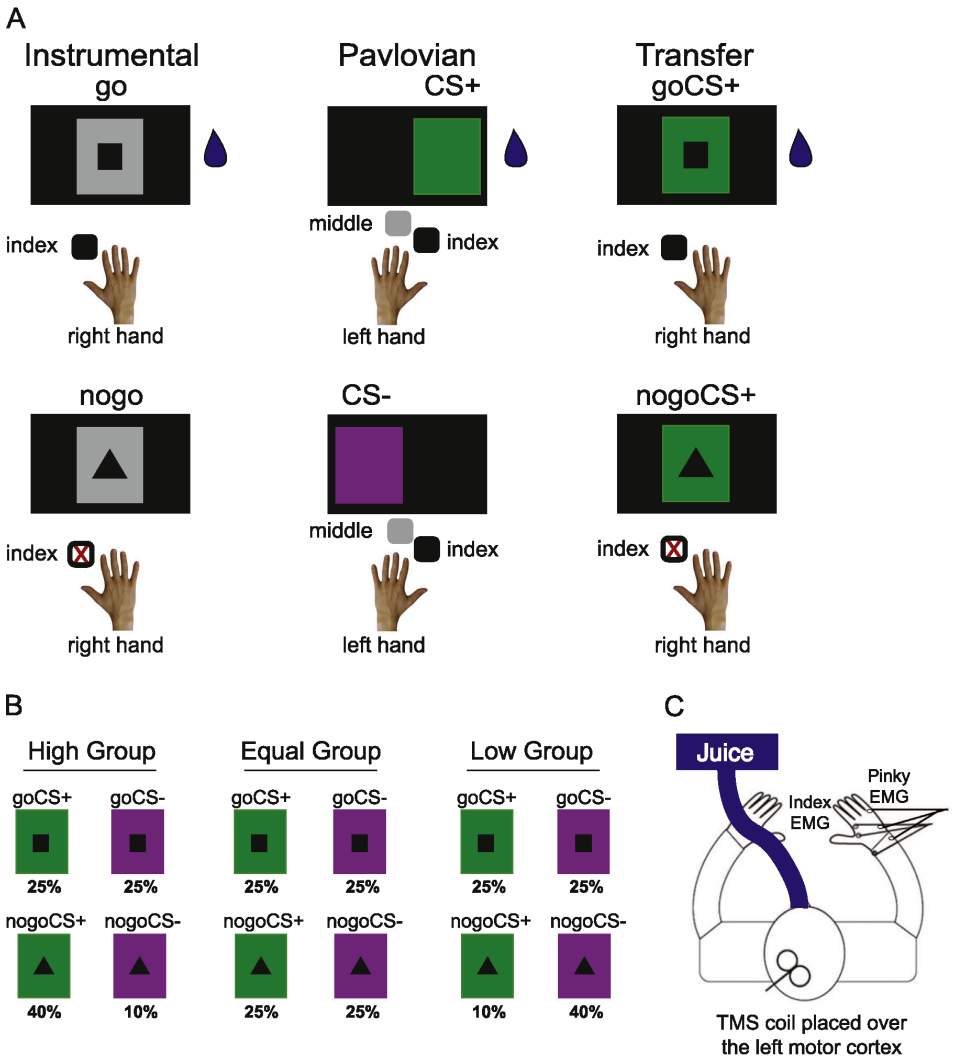

Fig. 1. Go-nogo/Pavlovian-to-instrumental transfer (PIT) task. (A) In the Instrumental phase, participants continuously pressed with the right index finger to obtain juice on go (square) trials. Juice delivery was based on a variable ratio reward schedule. On nogo (triangle) trials, no press was to be 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. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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 m 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-in. 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-in. 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 (Fig. 1C). 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) (Fig. 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 ml). 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 predetermined (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 go cue 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 the 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 (Fig. 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 the 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) (Fig. 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. RT 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 (High/Equal/Low) 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 Kruskall–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 faster 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 $Ps<0.001$), with faster RTs for CS+ compared to CS−. Importantly, the Stimulus × Group interaction was not significant ($F_{2,57}=2.11$, $p=0.13$), indicating no reliable 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 *t*-tests further confirmed no significant differences in conditioning between any of the groups (all $Ps>0.05$), 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+ versus 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, $\chi^2(2)=$

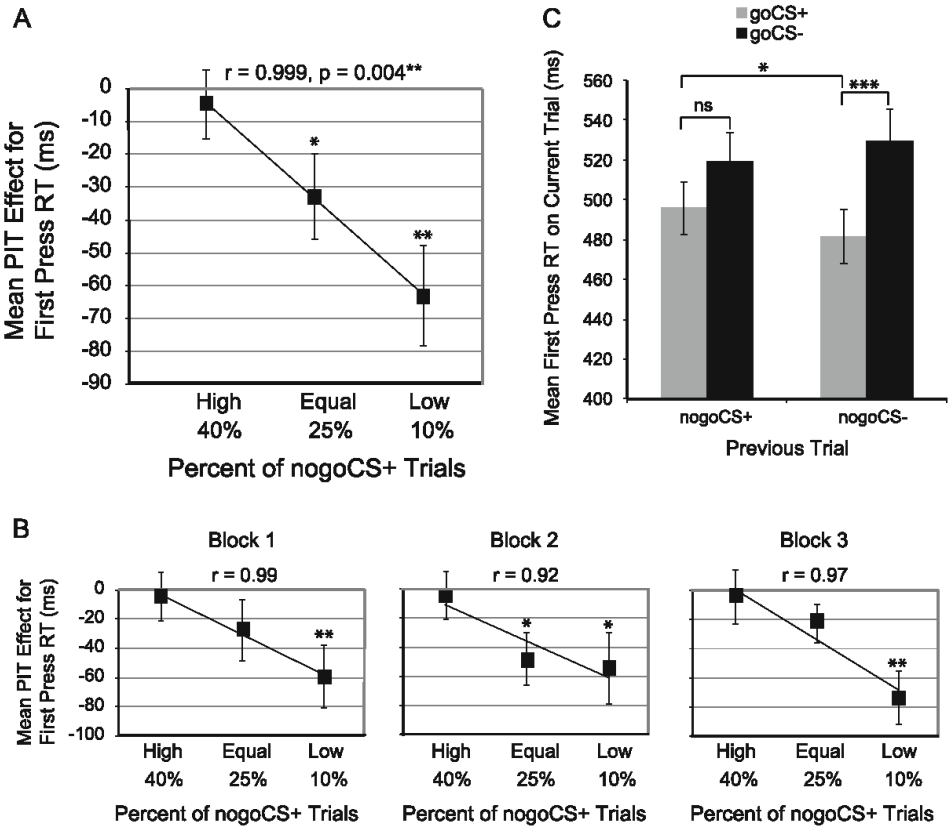

Fig. 2. Experiment 1 results. (A) Group PIT effects. The "PIT effect" represents mean goCS+ trials minus mean goCS− trials for first press RT in the Transfer phase. Across groups, an increase in the percentage of nogoCS+ trials corresponds to a decrease in the group PIT effect. (B) Relationship of group 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. $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$.

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 significant PIT effects ($Z=2.5$, $p=0.01$, $d=0.79$ and $Z=3.8$, $p<0.001$, $d=1.3$, respectively) (Fig. 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 $Ps > 0.05$), 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, $r=0.999$, $p=0.004$ (Fig. 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+ versus 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 (High/Equal/Low) as a between-subject factor. There was a main effect of Group ($F_{2,57}=4.54$, $p=0.01$), but no Block × 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 was modulated in the first block in the monotonic fashion of Low > Equal > High ($r=0.99$) (Fig. 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 (High/Equal/Low) as a between-subject factor showed no significant Time × 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.

4.2.4. 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-normally 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 × 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; $M_{\text{log-value}}=-0.75$, $\text{SD}_{\text{log-value}}=0.2$) versus nogoCS−, goCS− ($M=529$ ms, SD=123 ms; $M_{\text{log-value}}=-0.66$, $\text{SD}_{\text{log-value}}=0.21$), $Z=3.16$, $p=0.001$, $d=0.47$; while, there was no difference for nogoCS+,goCS+ ($M=496$ ms, SD=99 ms; $M_{\text{log-value}}=-0.72$, $\text{SD}_{\text{log-value}}=0.2$) versus nogoCS+,goCS− ($M=519$ ms, SD=113 ms; $M_{\text{log-value}}=-0.68$, $\text{SD}_{\text{log-value}}=0.19$), $Z=1.33$, n.s. (Fig. 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 current goCS+ trials alone, further analysis revealed slower first press RTs for nogoCS+,goCS+ compared to nogoCS−,goCS+ trials, $Z=2.0$, $p=0.045$, $d=0.21$ (Fig. 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 et al., 2005; Ridderinkhof, 2002; Stürmer et al., 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 et al., 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 equally-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

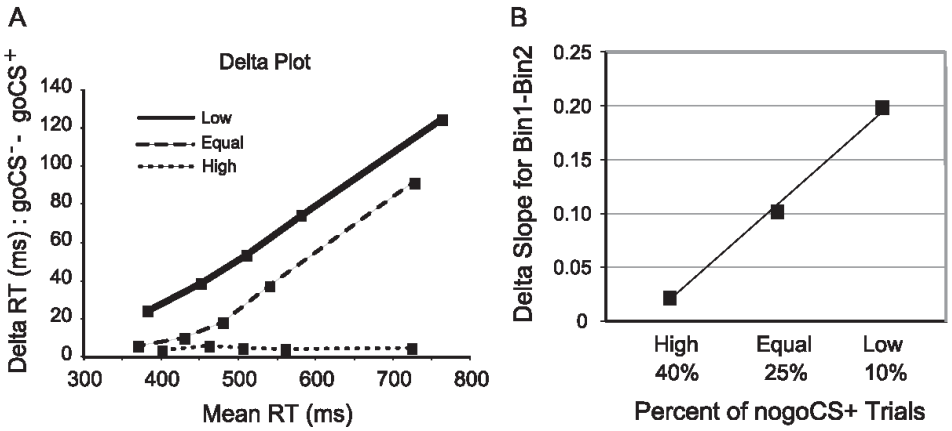

Fig. 3. Delta plots and early delta slopes from Experiment 1. (A) The delta RT (goCS− minus goCS+) is plotted against the mean RT for five time bins. Delta plots were significantly different across groups, with the High group showing evidence for response suppression on go trials. (B) Delta slope for 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.

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 × 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 (Fig. 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. 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 (Fig. 3B).

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 participants in the High group 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 potentially inappropriate action. 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 a sign of a response suppression control mechanism (Ridderinkhof et al., 2005). Consistent with this, a closer examination of the earliest time bins showed that the higher the proportion of nogoCS+ trials, the smaller the delta slope. This again suggests that a putative response control mechanism 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 (Fig. 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 a 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 (goCS+/goCS). 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 × 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. (Fig. 4A). We also found significantly slower first press RTs for nogoCS+,goCS+ compared to nogoCS−,goCS+ trials, $t_{13}=2.23$, $p=0.009$, $d=0.83$ (Fig. 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 × 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; $M_{\text{log-value}}=0.13$ mV, $SD_{\text{log-value}}=0.42$ mV) compared to nogoCS−,goCS− ($M=0.92$ mV, SD=0.30 mV; $M_{\text{log-value}}=-0.13$ mV, $SD_{\text{log-value}}=0.34$ mV), $Z=2.23$, $p=0.026$, $d=0.7$, yet no difference between nogoCS+,goCS+ ($M=0.94$ mV, SD=0.31 mV; $M_{\text{log-value}}=-0.11$ mV, $SD_{\text{log-value}}=0.30$ mV) and nogoCS+,goCS− ($M=1.01$ mV, SD=0.34 mV; $M_{\text{log-value}}=-0.04$ mV, $SD_{\text{log-value}}=0.34$ mV), $Z=0.72$, n.s. (Fig. 4B). Thus, evidence for the PIT effect (greater MEPs for goCS+ versus goCS−)

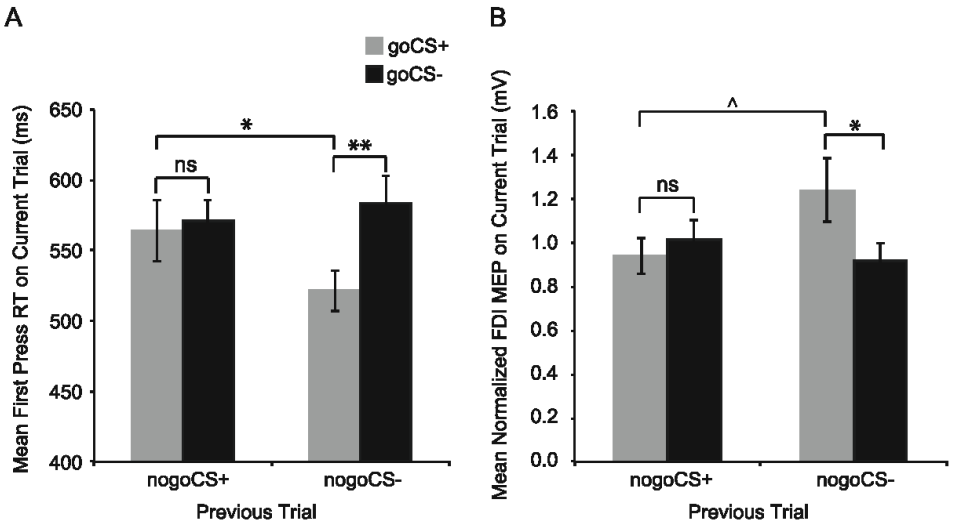

Fig. 4. Experiment 2 behavior and TMS. (A) First press RTs on current go trials as a function of previous trial type. RTs for goCS+ trials were significantly slower when following nogoCS+ (compared to nogoCS−) trials, replicating the trial-by-trial results in Experiment 1. (B) MEPs on current trial as 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. $^{**}p<0.01$, $^{*}p<0.05$, $p<0.06$.

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+ ($Z=1.91$, $p=0.056$, $d=0.52$) (Fig. 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 $Ps>0.22$), 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 (average RT: ~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 as 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 et al., 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 (CS+/CS-) 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 × 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; $M_{\text{log-value}}=-0.36$ mV, $SD_{\text{log-value}}=0.73$ mV) were significantly reduced compared to both nogoCS−,CS+ ($M=1.18$ mV, SD=0.63 mV; $M_{\text{log-value}}=0.05$ mV, $SD_{\text{log-value}}=0.49$ mV), $Z=2.06$, $p=0.04$, $d=0.48$, and nogoCS+,CS− ($M=1.25$ mV, SD=0.97 mV; $M_{\text{log-value}}=0.07$ mV, $SD_{\text{log-value}}=0.51$ mV), $Z=2.2$, $p=0.03$, $d=0.65$ (Fig. 5). Notably, because CS− trials were not influenced by previous nogoCS+ trials (as seen in Figs. 2C and 4A and B), the latter result suggests that motor activity on CS+ trials was suppressed (i.e. prevented from normal motor energization) when following nogoCS+ trials (Fig. 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 $Ps>0.28$), demonstrating that the above results were not contaminated by differences in the pre-TMS period.

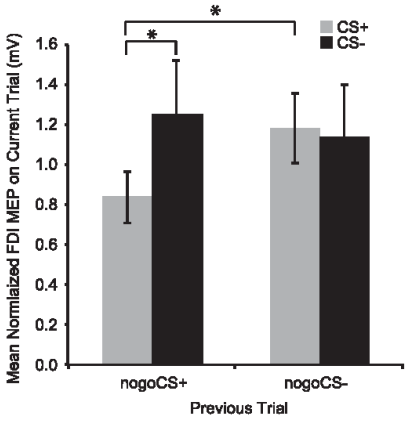

Fig. 5. Experiment 3 TMS results at 100 ms after stimulus onset. Current go and nogo trials were collapsed. Following nogoCS+ (compared to nogoCS−) trials, MEPs for CS+ were significantly reduced. MEPs for current CS+ trials were also reduced compared to current CS− trials when the previous trial type 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. *$p<0.05$.

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+ compared to both nogoCS−,CS+ and nogoCS+,CS− trials. Because CS− trials appear to be unaffected by previous nogoCS+ trials (Fig. 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.

All 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, $t_{16}=1.90$, $p=0.038$, $d=0.46$ (Fig. 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 (Fig. 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.).

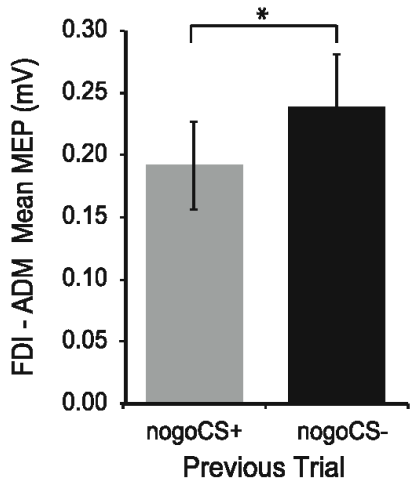

Fig. 6. Experiment 4 TMS results at 500 ms before stimulus onset. Difference scores were computed between the task-relevant FDI (index) muscle and the task-irrelevant ADM (pinky) muscle for previous trial types of nogoCS+ and nogoCS−. The ADM muscle served as a baseline control for non-specific physiological changes. There was significantly reduced FDI activity (relative to ADM) when the previous trial type was nogoCS+ compared to nogoCS−. *$p<0.05$.

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 higher proportion of nogoCS+ trials had smaller 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 early 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. Response suppression over a motivationally-triggered action tendency 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 that is specifically sensitive to the CS+.

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 et al., 2004; van Campen et al., 2013; see Fig. 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 et al., 2013; Zandbelt et al., 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 and Eriksen, 1974), Stroop (Stroop, 1935), and Simon tasks (Simon, 1969; Botvinick et al., 2004; Chen and Melara, 2009; Egner and Hirsch, 2005a, 2005b; Ullsperger et al., 2005). In these experiments, trials are considered to be "high-conflict" if there is incongruency 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

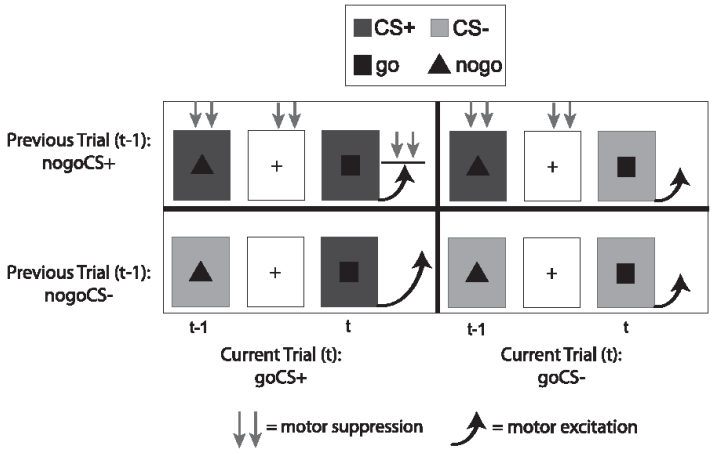

Fig. 7. A hypothesized model of the dynamics of response activation and suppression following nogoCS+ and nogoCS− trials. Following nogoCS+ trials (top two boxes), there is selective suppression of the task-relevant effector before the onset of the next trial. If the next trial is a CS+ (upper-left box), the suppressive influence is maintained 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 no suppression mechanism in place; as a result, there is quick motor energization for CS+ compared to CS− presentation.

appears on the left side of the screen; see Botvinick et al., 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 et al., 2001; Botvinick et al., 2004; Chen and Melara, 2009; Egner, 2007; but see Mayr et al., 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 and Hirsch, 2005a, 2005b; Egner, 2007; Kerns et al., 2004, but see Cohen Kadosh et al., 2011), or by putatively suppressing unwanted response tendencies, as in the Simon and Flanker tasks (Burle et al., 2014; Burle et al., 2004; van Campen et al., 2013; Pratte et al., 2010; Stürmer et al., 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 et al., 2014). 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 timepoint 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, which would enable such experiments to map 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 et al., 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.

Acknowledgements

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

Appendix A. Suplementary materials

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2015.01.016.

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Chapter 2, in full, is a reprint of the material as it appears in *Neuropsychologia*. Freeman, Scott M.; Alvernaz, Dominic; Tonnesen, Alexandra; Linderman, David; Aron, Adam, R., 2015. The dissertation author was the primary investigator and author of this paper.

Supplementary Tables

Table S2.1: Mean values for behavioral data in Experiment 1 for High, Equal, and Low groups. Values inside parentheses represent standard deviation.

Group	RTs (ms)		Number of Presses		Nogo Errors (%)	
	CS+	CS-	CS+	CS-	CS+	CS-
High (n=20)	528.9 (81.6)	533.7 (85.2)	14.00 (1.7)	14.03 (1.9)	4.37 (5.5)	2.92 (5.6)
Equal (n=20)	493.2 (82.0)	526.0 (67.9)	13.89 (1.9)	13.76 (1.8)	4.17 (5.39)	2.67 (3.52)
Low (n=20)	507.4 (102.1)	570.5 (142.6)	13.88 (1.3)	13.30 (1.8)	4.17 (5.74)	1.35 (2.17)

Table S2.2: Mean values for behavioral data in Experiments 2-4. Values inside parentheses represent standard deviation.

Experiment	**RTs (ms)**		**Number of Presses**		**Nogo Errors (%)**	
	CS+	**CS-**	**CS+**	**CS-**	**CS+**	**CS-**
2 (n=14)	547.9 (55.6)	576.1 (49.6)	14.12 (1.5)	14.04 (1.5)	3.9 (5.4)	1.3 (2.1)
3 (n=13)	669.1 (142.0)	709 (155.6)	11.37 (1.63)	11.33 (1.86)	0.96 (3.4)	0 (0)
4 (n=17)	534.9 (71.1)	553.5 (83.6)	11.3 (1.88)	11.14 (1.82)	2.49 (3.83)	0.68 (1.51)

Table S2.3: Mean raw CSE values (in mV) for the TMS data in Experiment 2. Values outside parentheses represent standard deviation.

	FDI
nogoCS+,goCS+	0.58 (0.21)
nogoCS-,goCS+	0.73 (0.31)
nogoCS+,goCS-	0.61 (0.25)
nogoCS-,goCS-	0.55 (0.20)
Null Baseline	0.62 (0.22)

Table S2.4: Mean raw CSE values (in mV) for the TMS data in Experiment 3. Values inside parentheses represent standard deviation.

	FDI
nogoCS+,CS+	0.40 (0.20)
nogoCS-,CS+	0.58 (0.28)
nogoCS+CS-	0.55 (0.19)
nogoCS-,CS-	0.50 (0.30)
Null Baseline	0.53 (0.20)

Table S2.5: Mean raw CSE values (in mV) for the TMS data in Experiment 4. Values inside parentheses represent standard deviation.

	FDI	**ADM**
nogoCS+	0.46 (0.17)	0.27 (0.14)
nogoCS-	0.50 (0.22)	0.26 (0.15)

CHAPTER 3

The Pavlovian-to-instrumental transfer effect is diminished in individuals with high reward eating drive

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Manuscript in preparation for publication

ABSTRACT

In today's obesogenic environment, where food is readily available, highly palatable, inexpensive, and calorically dense, it is important for people to control their impulses to eat once nutritional needs have been met. Two factors that likely influence the ability to control such impulses are being excessively motivated towards food rewards and impaired response control in the face of such provocations. We examined these two factors (level of motivation) and (response control) with a behavioral task in 34 human participants who varied significantly in weight and eating drive. The task required people to respond rapidly (go) and sometimes to withhold (nogo) in the face of a high provocation or low provocation stimulus. There were no differences between groups when stratified on Body Mass Index. However, when stratified on a questionnaire-based measure of reward eating drive, we found that those people with a high (versus low) reward eating drive were less provoked by the high provocation stimulus. Subsequent analyses suggested that the reduced provocation developed over time and was possibly due to more control prior to the onset of each trial. We speculate that people with high reward eating drive need to compensate for deficient reactive control mechanism by putting in place a "proactive control" system before the food-related stimulus occurs. This proactive system may operate at the response level.

INTRODUCTION

Controlling the impulse to eat in the face of food cues is difficult in today's obesogenic environment, where food is readily available, highly palatable, inexpensive, and calorically dense. For some, controlling such impulses requires little effort. For others, it becomes a lifelong struggle that consumes time and energy. Failing to control such impulses (at least once nutritional needs are met) can lead to worrisome conditions, such as obesity (Appelhans, 2009; Epel et al., 2014; van den Bos & de Ridder, 2006) and eating disorders (Dawe & Loxton, 2004; Wu et al., 2013). It is therefore important to develop a better understanding of how reward-driven impulses are controlled and why such control is more difficult for some than others.

One reason that some individuals may struggle with controlling provocations from food cues is that their motivational drive for food rewards is heightened. Indeed, a number of studies have found that obesity and overeating are related to excessive motivational drive, sometimes referred to as "hedonic hunger" (Lowe & Butryn, 2007; Mela, 2006; Schag, Schonleber, Teufel, Zipfel, & Giel, 2013; Schultes, Ernst, Wilms, Thurnheer, & Hallschmid, 2010). High levels of "hedonic hunger" are thought to result from a heightened "wanting" of palatable foods, while the actual "liking" of foods plays a less significant role (Appelhans, 2009; Berridge & Robinson, 2003; Mela, 2006). A second reason individuals may struggle is that their ability to control reward-driven actions is diminished. Consistent with this, several studies have found that overweight and obese individuals are slower to stop actions towards food-related stimuli (Chamberlain, Derbyshire, Leppink, & Grant, 2015; Mole et al., 2014; Nederkoorn,

Coelho, Guerrieri, Houben, & Jansen, 2012). Taken together, a "hedonic-inhibitory" model has been proposed (Appelhans, 2009; Stice & Yokum, 2016), in which overconsumption of tasty foods results from a combination of excessive appetitive motivation and impaired motor response control processes.

To better understand if and how appetitive motivation and response control are altered in people with varying weights and reward sensitivity, we used our recently developed paradigm that manipulates both the reward-driven provocation (high vs. low provocation) and the action requirement (respond for the reward vs. withhold the response). Specifically, our task combines an associative learning phenomenon in which a conditioned stimulus motivates instrumental behavior—called Pavlovian-to-instrumental transfer (PIT)—with a go-nogo task. This hybrid paradigm creates a situation where provocation by the food cue is beneficial on go trials (since more pressing leads to a greater chance of getting the reward), yet "dangerous" on nogo trials (due to an increased chance of pressing inappropriately). As in previous PIT experiments, there were three phases (Bray, Rangel, Shimojo, Balleine, & O'Doherty, 2008; Corbit & Balleine, 2005; Corbit, Janak, & Balleine, 2007; Prévost, Liljeholm, Tyszka, & O'Doherty, 2012) (Figure 1). In the Instrumental phase, participants continuously pressed a button on go trials and withheld responding on nogo trials. If they pressed enough times on a go trial, they received a small drop of chocolate or vanilla-flavored milk (whatever they preferred). In the Pavlovian phase, they learned to associate one color (green or purple) with milk delivery (CS+) and the other color with no milk delivery (CS-). The Transfer phase is the key part of the paradigm. Here the Palvovian influence is combined

with the go/nogo requirement. Again, on go trials, participants pressed to get milk[1], but now with a motivating (CS+) or non-motivating (CS-) stimulus in the background; while, on nogo trials, responding was to be withheld in the presence of CS+ or CS-. The PIT effect is quantified using three dependent measures from the Transfer phase: 1) reaction time of the first press (henceforth referred to as first press RT), 2) number of presses, and 3) percentage of errors on nogo trials (Freeman, Alvernaz, Tonnesen, Linderman, & Aron, 2015; Freeman, Razhas, & Aron, 2014). The first press RT captures early provocation, the number of presses indicates the amount of sustained motivation on go trials, and nogo errors index the control over the provocation. Previous studies have found that the presence of the CS+ (versus CS-) leads to faster and more pressing on go trials, as well as more errors on nogo trials—all of which reflect a "PIT effect" (Freeman et al., 2015, 2014).

To examine how the provocation and control differ across individuals, we recruited participants across a wide range of BMI scores. We then grouped the participants by their BMI scores as healthy-weight, overweight, and obese, and tested for potential group differences in PIT effects. In other analyses, we stratified participants based on questionnaires that are related to BMI, but may be better at detecting individual differences in reward sensitivity. We did this for the Reward-Based Eating Drive (RED) and the Behavioral Inhibition System / Behavioral Activation System (BIS/BAS) questionnaires.

[1] In traditional PIT experiments, the Transfer phase is done in extinction (no reward). Here, the milk reward continued to be delivered to maintain a high level of motivation, which was critical for the study's goals.

MATERIALS AND METHODS

Participants

Forty volunteers (twelve males) were recruited from listserves and advertisements in the San Diego community (mean age = 37.7, *SD* = 11.3). All participants were right-handed, 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 pump system, leaving a total of 38 participants. This study was approved by the UCSD Institutional Review Board.

Stimuli and procedure

Screening process

Interested participants completed an online screen consisting of the CAGE-AID (Brown, Leonard, Saunders, & Papasouliotis, 2001), Overall Anxiety Severity and Impairment Scale (OASIS) (Norman, Cissell, Means-Christensen, & Stein, 2006), and Patient Health Questionnaire-9 (PHQ-9) (Kroenke, Spitzer, & Williams, 2001) to initially screen out substance abuse, anxiety, and depression, respectively. Participants were excluded if they scored a 2 or greater on the CAGE-AID, 8 or greater on the OASIS, or 15 or greater on the PHQ-9.

Those that passed the online screening completed a phone interview to further evaluate exclusionary criteria. Exclusion criteria for the phone interview included the reporting of 1) a psychiatric disorder diagnoses, 2) a diagnosis of a serious physical

disease for which physician supervision of diet and exercise prescription were needed, 3) currently taking medications that would influence weight and eating, and 4) any history of an eating disorder.

Procedure

Upon arrival, participants read an information sheet, provided written consent, and completed two motivation-based questionnaires: Motivation for Milk and the Hunger and Fullness questionnaires. While these were being completed, the experimenter filled a syringe with approximately 65 mL of the selected milk and placed the syringe in the milk pump. The types of milk used were Silk Almond Dark Chocolate milk and Silk Almond Vanilla milk. The milks were matched on caloric intake. Milk 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 participants with a rubbing alcohol pad before the experiment began. Throughout the experiment, approximately one inch of tubing rested comfortably in the mouth of the participant. Milk delivery was triggered via customized Matlab scripts.

Participants then had their height and weight measured, which was followed by the go-nogo/PIT task. During the task, participants sat in front of a 51-inch Dell monitor (60 Hz refresh rate) and made responses on a button pad that was placed approximately 12-inches from the monitor. In between the Pavlovian and Transfer phases of the task, participants completed another Motivation for Milk Questionnaire to investigate potential

changes in motivation. Following the task, participants completed a similar task involving money to evaluate if any observed group differences in the PIT effect is general to other rewards or food specific. Finally, after completing all the tasks, the participants completed the RED and BIS/BAS questionnaires.

Go-nogo/Pavlovian-to-instrumental transfer (PIT) task

The PIT task 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 1). For each participant, one shape was randomly selected as the go cue and the other the nogo cue. Upon presentation of the go cue, participants could continuously press a button during the duration of the go trial (2.5 s) with his or her right index finger to obtain a drop of milk (0.5 milliliters). Milk was delivered on a variable ratio reward schedule (8-14 presses; 11 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 milk 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 milk delivery on a given trial, a small black circle appeared above the square to signify imminent milk 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 milk delivery, which was important for the Transfer phase. 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. The relatively long ITI was chosen to allow enough time for swallowing of the liquid. 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 1). 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 milk delivery (CS+), while the other color was always associated with no milk delivery (CS-). The CS+ and CS- colors were counterbalanced across participants. For CS+ trials, milk was always delivered 1.5 s after stimulus onset and the rectangle remained on the screen for an additional 1 s for a total trial duration of 2.5 s. Participants were instructed that milk 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 milk 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 three exceptions. First, there was no longer a black circle to indicate impending milk delivery. This encouraged participants to keep pressing throughout the trial because they did not know if milk would be delivered. Participants had a general idea of the number of presses needed for milk delivery based on the Instrumental phase. Second, the Transfer phase had three blocks, each consisting of 48 trials (144 total trials). This allowed for a sufficient number of trials per condition, but was brief enough to avoid satiation (see Freeman et al., 2014). 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-.

Money Task

We used the money task of Freeman and Aron (2015), which is similar to the go-nogo/PIT task. The key differences in this task are as follows: 1) instead of milk, participants pressed to earn points, which converted to money at the end of the experiment; 2) the background color (blue or yellow now) was task-relevant in the sense that it indicated to the participant if they could earn a lot of points on that trial (high value) or very few points (low value); 3) there were not three phases of the task; instead, participant learned the high/low value point association in the first block, which was designated a “learning block” and excluded from the analysis (for all other details, refer to Freeman & Aron, 2015).

Measures

Motivation for Milk. This questionnaire surveyed 1) the number of hours since the last consumption of liquid, 2) the type of milk that the participant preferred to consume throughout the experiment (there were two possible milk types: chocolate or vanilla flavored milk), 3) the participant's thirst level (1-7 Likert scale; 1 – Not at all, 7 – Extremely), 4) how much the participant liked the milk that he or she selected (1-7 Likert scale; 1 – Very little, 7 – Very much), and 5) how much the participant wanted the milk at that moment (1-7 Likert scale; 1 – Not at all, 7 – A lot).

Hunger and Fullness. This questionnaire surveyed 1) the participant's hunger level (1-5 Likert scale; 1 – Not at all, 5 – Extremely hungry), 2) how much food the participant could eat at that moment (1-5 Likert scale; 1 – Nothing at all, 5 – A large amount), 3) how full the participant felt (1-5 Likert scale; 1 – Not at all, 5 – Extremely full), and 4) how full the participant's stomach was at that moment (1 = Empty, 2 = Half full, 3 = Full).

Reward-Based Eating Drive (RED). The RED questionnaire was developed by Epel et al. (2014) to target reward-based eating drive in a non-pathological population. It has nine total questions, with four taken from the Three-Factor Eating Questionnaire (Stunkard & Messick, 1985), two taken from the Binge Eating Scale (gormally, Black, Daston, & Rardin, 1982), and three original questions. RED scores have high internal consistency (Cronbach's $\alpha = 0.82$), low skewness, low kurtosis, and predictive validity for weight gain (Epel et al., 2014). It captures overlapping, but non-identical constructs as the Yale Food Addiction Scale ($r^2 = 0.25$) and the Power of Food Scale ($r^2 = 0.49$) and is

independently predictive of BMI (Epel et al., 2014). Factor analysis showed that the RED scale is comprised of three sub-categories: 1) lack of control, 2) lack of satiation, and 3) preoccupation with food.

Behavioral Inhibition System / Behavioral Activation System questionnaire. The behavioral inhibition system (BIS) reflects sensitivity to punishment and avoidance motivation. In contrast, the behavioral activation system (BAS) reflects sensitivity to reward and approach motivation (Gray, 1981). In 1994, Carver & White developed a BIS/BAS scale to measure these contrasting systems. Factor analysis showed that the questionnaire contains four basic factor loadings: 1) BIS – anticipation of punishment, 2) BAS-Drive – pursuing desired rewards, 3) BAS-Fun Seeking – desiring and impulsively approaching new rewards, and 4) BAS-Reward Responsiveness – anticipation of reward (Carver & White, 1994).

Anthropometry. Height was measured using a stadiometer and weight was measured using a Tanita scale after participants removed jackets, outerwear, and shoes. Each measurement was completed three times by trained study staff; the average was used for analysis. The height and weight values were converted into a body mass index (BMI) score and recorded by the experimenter.

Analysis

BMI grouping

We grouped the participants according to their BMI score, such that a score of 18.5-24.9 = healthy-weight; 25-29.9 = overweight; 30.0 and above = obese. The group

sizes for healthy-weight, overweight, and obese were: n = 14, n = 13, and n = 11, respectively. There were no significant group differences in Age or Gender (*P*s > 0.05).

RED grouping

We split the RED scores into Low and High groups using a median split (median = 11). Because four participants had RED scores equal to the median, we excluded those four participants from the analysis, thus allowing a distinct division between Low and High RED individuals. This yielded 34 participants for the analysis: 17 Low and 17 High. There were no significant group differences in Age or Gender (*P*s > 0.05).

BIS/BAS grouping

BIS. We split the BIS scores into Low and High groups using a median split (median = 19.4). We excluded two participants who had a BIS score of 19, which was nearly the median. This yielded 36 participants for the analysis: 17 Low, 19 High. There were no significant group differences in Age or Gender (*P*s > 0.05).

BAS-fun seeking. We split the BAS-fun seeking scores into Low and High groups using a median split (median = 11.6). We excluded eight participants who all had a BAS-fun seeking score of 12, which was nearly the median. This yielded 31 participants for the analysis: 14 Low, 16 High. There were no significant group differences in Age or Gender (*P*s > 0.05).

BAS-drive. We split the BAS-drive scores into Low and High groups using a median split (median = 11.6). We excluded eight participants who had all had a BAS-drive score of 12, which was nearly the median. This yielded 30 participants for the

analysis: 16 Low, 14 High. There were no significant group differences in Age or Gender (*P*s > 0.05).

BAS-reward responsiveness. We split the BAS-reward responsiveness scores into Low and High groups using a median split (median = 17.8). We excluded six participants who had all had a BAS-drive score of 18, which was nearly the median. This yielded 32 participants for the analysis: 15 Low, 17 High. There were no significant group differences in Age or Gender (*P*s > 0.05).

PIT effects

Our primary dependent measures involved the motor provocation generated by the motivating stimulus (CS+) compared to the non-motivating stimulus (CS-) during the Transfer phase (i.e. the PIT effect). We specifically focused on 1) median reaction time to the first press on go trials (henceforth called first press RT), 2) number of presses on go trials, and 3) the percentage of commission errors on nogo trials. Trials were excluded if first press RT was less than 100 ms or if a response was not made on a go trial. Values were entered into a mixed-model ANOVA with Stimulus (CS+/CS-) as a within-subject factor and Group as a between-subject factor. Importantly, a significant Stimulus x Group interaction indicated a group difference in the PIT effect, which was the primary interest of the study.

Money task

Similar to the PIT task, we compared high reward and low reward trials using three dependent measures: (1) first press RT on go trials, 2) number of presses on go trials, and (3) the percentage of commission errors on nogo trials. As the first block was

considered a "learning block" (where participants learned the color-reward associations), these trials were excluded from the analysis. Trials were also excluded if first press RT was less than 100 ms or if a response was not made on a go trial. Values were entered into a mixed-model ANOVA with Stimulus (high reward/low reward) as a within-subject factor and Group as a between-subject factor. As in the go-nogo/PIT task, a significant Stimulus x Group interaction indicated a group difference in sensitivity to the high reward stimulus.

RESULTS

PIT effects

The key effect of interest was a significant Group x Stimulus interaction. This would indicate that the strength of the PIT effect (CS+ minus CS-) differs across groups, which was the main investigation of the study. Below we analyze PIT effects across groups for BMI, RED, BIS, BAS-fun seeking, BAS-drive, and BAS-reward responsiveness. For all analyses, we ran ANOVAs with the factors of Group and Stimulus, for each of the three PIT measures: 1) first press RT, 2) number of presses, and 3) nogo errors.

Body mass Index (BMI)

For first press RT, number of presses, and nogo errors, there were no significant main effects or interactions (all *P*s > 0.05). We repeated the analysis when overweight and obese groups were collapsed to examine any differences between individuals within

the healthy weight range and individuals above the healthy weight range, but still did not find a significant Stimulus x Group interaction.

Reward-based eating drive (RED)

For first press RT, there was a significant main effect of Stimulus ($F_{1,32} = 4.86$, $p = 0.03$), whereby faster responses were made in the presence of the CS+ (compared to the CS-) stimulus, as seen in several studies (Freeman et al., 2014, Freeman et al., 2015). There was also a significant Stimulus x Group interaction ($F_{1,32} = 6.13$, $p = 0.02$). Surprisingly, post-hoc *t*-tests revealed a significant PIT effect for the Low RED group ($t_{16} = 4.81$, $p < 0.001$), but not for the High RED group ($t < 1$) (Figure 2A). This was driven by a slowing of the CS+ stimulus in the High RED group, while the CS- RTs were comparable across the two groups. The interaction remained significant when BMI was added to the model as covariate ($p = 0.03$), suggesting that RED scores are independently related to the reaction time PIT effect.

For number of presses, there was also a significant main effect of Stimulus ($F_{1,32} = 5.1$, $p = 0.03$), whereby more presses were made in the presence of the CS+ stimulus. There was a main effect of Group ($F_{1,32} = 5.00$, $p = 0.03$), with the Low RED group showing a greater number of presses than the High RED group, but the Stimulus x Group interaction was not significant ($F_{1,32} = 2.03$, $p = 0.16$).

Finally, for nogo error rate, there were no significant main effects or interactions, all *P*s > 0.05 (Figure 2C).

Behavioral inhibition system / Behavioral activation system

BIS. For first press RT, number of presses, and nogo errors, there were no significant main effects or interactions (all *P*s > 0.05).

BAS-fun seeking. For first press RT and nogo errors, there was a main effect of Stimulus (RT: $F_{1,28} = 6.79$, $p = 0.01$; Error: $F_{1,28} = 5.32$, $p = 0.03$), whereby RTs were faster and more errors were made with the CS+ (compared to CS-) in the background. No other main effects or interactions were significant for any of the three dependent measures (all *P*s > 0.05).

BAS-drive. For first press RT, there was a significant main effect of Group ($F_{1,28} = 5.68$, $p = 0.02$), whereby RTs in the High BAS-drive group were significantly slower. No other main effects or interactions were significant for any of the three dependent measures (all *P*s > 0.05).

BAS-reward responsiveness. For first press RT, number of presses, and nogo errors, there was a main effect of Stimulus (RT: $F_{1,30} = 5.75$, $p = 0.02$; Presses: $F_{1,30} = 4.3$, $p = 0.047$; Errors: $F_{1,30} = 5.21$, $p = 0.03$), whereby RTs were faster, more presses were made, and nogo commission errors were committed with the CS+ (compared to CS-) in the background. There was also a significant main effect of Group for number of presses ($F_{1,30} = 4.85$, $p = 0.04$), with the High group pressing less than the Low group. There were no significant interactions for any of the three dependent measures (all *P*s > 0.05).

Money task

For first press RT, across all groupings (BMI, RED, and BAS/BIS), there was a significant main effect of Stimulus, such that RTs were significantly faster to the high versus low reward stimulus (all *P*s < 0.001), as expected (Freeman & Aron, 2015). However, there were no main effects of Group, nor were there any Stimulus x Group interactions (all *P*s > 0.05). The same pattern was present for number of presses and nogo errors.

Follow-up RED analyses

Thirst and hunger validation analysis

To verify that the two RED groups were not significantly different in their baseline levels of motivation for the milk reward, we compared High and Low RED groups on 1) the number of hours since the last consumption of liquid and food, 2) thirst level, 3) liking of the milk, 4) wanting of the milk, 5) hunger level, 6) amount of food that he/she could eat at that moment, and 7) stomach "fullness" using t-tests. There were no significant group differences for any of the hunger or thirst measures prior to the experiment or immediately before the transfer phase (all *P*s > 0.05; data not displayed). Thus, the slower reaction time PIT effect we observed in the High RED group was not due to basic differences in motivation levels.

Pavlovian conditioning

We also tested whether there were basic differences in Pavlovian conditioning across Low and High RED groups. We analyzed median reaction times (RTs) for CS+ and CS- trials during the Pavlovian phase. Note that the CS+ and CS- colors were

irrelevant during this phase, but previous studies have shown that participants are nevertheless more energized in the presence of the CS+, resulting in faster RTs (Freeman et al., 2015, 2014). Just as in the PIT effect analysis, all trials that were either incorrect trials or had a RT of less than 100 ms were excluded from the analysis. There was a script malfunction for one participant in the High RED group so this participant was excluded for this analysis. Results showed a significant main effect of Stimulus ($F_{1,31} = 9.06$, $p = 0.005$), but no main effect of Group or Stimulus x Group interaction (Fs < 1). *T*-tests showed evidence of Pavlovian conditioning (faster CS+ versus CS- RT) in both groups (Low: $t_{16} = 2.06$, $p = 0.028$; High: $t_{15} = 2.56$, $p = 0.02$). Thus, there appear to be no group differences with regard to learning the Pavlovian associations.

Reaction time PIT effect across blocks

A key result from above was that the reaction time (RT) PIT effect was absent in the High RED group – i.e. people with high reward eating drive did not respond more quickly for a CS+ (predictive of a high coloric milk reward) versus a CS- stimulus.

To probe further, we asked if the absent RT PIT effect in the High RED group occurred from the beginning of the Transfer phase, or if it diminished across time. Because our primary focus was the slowing of the CS+ stimulus, we analyzed the first press RTs for the CS+ and CS- stimuli separately, with the prediction that any slowing across blocks should only occur with the CS+ stimulus. Thus, for each stimulus type, we used mixed ANOVAs with Block (B1/B2/B3) as a within-subject variable and Group (High/Low) as a between-subject variable.

For the CS+ stimulus, there was a main effect of Block ($F_{2,64} = 3.4$, $p = 0.04$) with an overall pattern of slower responding across the three blocks (B1 = 485 ms, B2 = 498 ms, B3 = 508 ms) (Figure 3A). There was also a marginally significant Group x Block interaction ($F_{2,64} = 2.5$, $p = 0.09$), whereby CS+ RTs in the High RED group slowed down across time. Interestingly, the average CS+ RTs in the High RED group slowed down in a nearly monotonic fashion across the three blocks (B1 to B2: 16 ms decrease; B2 to B3: 19 ms decrease) (Figure 3A). For the CS- stimulus, there were no significant main effects or interactions (Ps > 0.8) (Figure 3B).

For exploratory purposes, we compared the RT PIT effect (CS+ RT minus CS- RT) across blocks for both groups. This analysis showed no significant difference in the PIT effect for Block 1 ($t < 1$), a marginally significant difference for Block 2 ($t_{32} = 1.73$, $p = 0.09$), and a significance difference for Block 3 ($t_{32} = 2.11$, $p = 0.02$) (Figure 3C). This suggests that the group differences in the RT PIT effect really emerged in Blocks 2 and 3.

Trial-by-trial proactive control

One explanation for the group differences in the RT PIT effect is that High RED individuals adopted a more proactive strategy throughout the course of the experiment to help mitigate inappropriate provocation on nogoCS+ trials. For example, prior to each trial, they could amplify their attentional focus on the go/nogo cue or proactively suppress their responding hand. To explore what type of proactive control may have been implemented, we conducted a new analysis that a previous study used to demonstrate proactive response suppression using the same go-nogo/PIT task (Freeman et al., 2015). That study found that, if the previous trial was a nogoCS+ trial, participants were no

longer more provoked by a subsequent CS+ stimulus—which manifested behaviorally in longer first press RTs for the CS+ (Figure 4A). Importantly, it showed that the reduced provocation following nogoCS+ trials was due to a response suppression mechanism that was in place before the onset of the next trial. It was hypothesized that the proactive suppression occurred because nogoCS+ trials are potentially "dangerous" trials that increase the current awareness of the need to control the CS+ provocation. It is therefore possible that High RED individuals have a heightened awareness for the need to mitigate potential provocation. This predicts that High RED individuals implement proactive control following nogoCS+ *and* nogoCS- trials, while Low RED individuals implement proactive control only following nogoCS+ trials (as was previously observed). To examine this, we conducted an exploratory analysis to detect potential group differences in first press RTs on current goCS+ and goCS- trials when following a nogoCS+ or nogoCS- trial type. Because our primary focus was group differences following nogoCS- trials, nogoCS- and nogoCS+ were analyzed separately. Also, we focused only on Blocks 2 and 3 of the Transfer phase, since this is when the RT PIT effect diverged across RED groups.

For both groups, the PIT effect was absent following nogoCS+ trials ($t < 1$ for both groups). However, following nogoCS- trials, there was a significant Group x Trial interaction ($F_{1,32} = 4.45$, $p = 0.043$), in which the Low RED group showed a significant PIT effect (i.e. following nogoCS- trials, they were more provoked by the CS+ compared to the CS-; $t_{16} = 2.73$, $p = 0.015$) (Figure 4B), while the High RED group again showed an absent PIT effect ($t < 1$) (Figure 4C). These results are consistent with the idea that the

High RED group implemented proactive motor suppression following *both* nogoCS+ and nogoCS- trials.

DISCUSSION

We examined how reward-driven provocation and the control over that provocation differ across individuals with varying weights and reward sensitivity. To test this, we used a hybrid Pavlovian-to-instrumental transfer (PIT)/go-nogo task, in which being provoked by the Pavlovian stimulus (the CS+) is beneficial on go trials (since more pressing means a greater chance of getting the reward), yet 'dangerous' on nogo trials (due to an increased chance of pressing inappropriately). We tested for differences in the PIT effect (CS+ minus CS-) for first press RT, number of presses, and nogo errors. When comparing healthy-weight, overweight, and obese individuals, our results showed no significant group differences in any of the PIT effect measures. The same was true when we compared individuals based on their BIS/BAS scores. However, when we compared individuals who were Low versus High on the reward-based eating drive (RED) scale, we found that the first press RT on goCS+ trials was significantly slower in the High RED group, indicating that the immediate provocation induced by the CS+ was diminished in high RED individuals. Further analyses showed that the RT slowing in the High RED group 1) emerged across time, 2) was not driven by group differences in baseline motivational drive or Pavlovian conditioning, and 3) was specific to cues that predicted food.

A "Proactive" Account

The reduced CS+ provocation in the High RED group is not the most intuitive result, as one might expect that individuals with a high reward eating drive would show greater sensitivity to the CS+ stimulus. However, in this task, CS+ provocation is maladaptive on nogo trials, particularly if there is any deficiency in the ability to reactively suppress the provocation. We propose that the reduced provocation in the High RED group is consistent with the hypothesis that High RED individuals adopt a safer, more proactive strategy throughout the course of the experiment to help mitigate inappropriate provocation on nogoCS+ trials. Shifting from a reactive to proactive control strategy has been found in many previous studies using different types of tasks. For example, studies using a modified stop signal task have found that increasing the expectancy of stop signals leads to greater use of proactive control, manifesting in higher response thresholds and RT slowing (Stuphorn & Emeric, 2012; Verbruggen & Logan, 2008, 2010; Zandbelt, Bloemendaal, Hoogendam, Kahn, & Vink, 2013; Zandbelt, Bloemendaal, Neggers, et al., 2013). Other studies using reward-based working memory paradigms have found that the shift towards proactive control depends on reward sensitivity, such that individuals with high reward sensitivity are more likely to use proactive control in a high reward context (Braver, 2012; Jimura, Locke, & Braver, 2010).

Here, we postulate that High RED individuals struggled to reactively control the provoked action tendency, resulting in a shift towards proactive control and longer RTs. This suggests that proactive control may be a powerful strategy to mitigate provocations that can be maladaptive. It also highlights how task context, trait differences, and the type

of control (e.g., proactive vs. reactive) are all important factors to consider in an experimental paradigm.

Potential Mechanisms

While the "Proactive" account assumes a shift to a more proactive control strategy, it is unclear what type of control mechanism was used. One possibility is that, during the ITI period, participants focused their attention more towards the center of the screen (i.e. at the location of the go or nogo cue) to avoid being provoked by the background CS+ stimulus (Harris et al., 2013; Langford, Krebs, Talsma, Woldorff, & Boehler, 2016). Another possibility is that participants proactively suppressed their right index finger (i.e. the relevant response channel during the ITI period; (Cai, Oldenkamp, & Aron, 2011; Freeman et al., 2015; Majid, Cai, Corey-Bloom, & Aron, 2013) and sustained the suppression until a decision threshold was reached to allow pressing on a go trial.

Although we could not test the mechanism directly, we conducted an exploratory analysis that provided some clues. The exploratory analysis was based on a previous study that used the same go-nogo/PIT task (Freeman et al., 2015). The study showed that, only when following nogoCS+ trials, goCS+ RTs were slower and that the slowing was due to proactive response suppression in the task-relevant effector after nogoCS+ trials. It was hypothesized that nogoCS+ trials are particularly viewed as "dangerous" trials that increase the current awareness of the need for control. In our exploratory analysis, we examined if High RED individuals would show the goCS+ slowing following both nogoCS+ and nogoCS- trials, rather than only following nogoCS+ trials. Indeed, this turned out to be the case: goCS+ RT for the High RED group was slower following both

nogoCS+ and nogoCS-, while goCS+ RT for the Low RED group was only slower following nogoCS+ trials. While it is only an inference, this suggests that High RED individuals used proactive response suppression to mitigate CS+ provocation.

Limitations and remaining questions

There are several limitations to this study. First, many analyses were run for many different measures (i.e. ANOVAs for three PIT measures separately for each of BMI, RED, and three BIS/BAS variables) with numerous post-hoc tests. We did not correct the *p*-values for all these comparisons. This is the first study of its kind using the hybrid go-nogo/PIT task, though in only a moderately sized sample. We regard the results as preliminary, requiring confirmation in a larger sample. Second, while we speculate that the high RED group shifted to a proactive control strategy, this is a post-hoc interpretation that cannot be directly tested in the study. An alternative is that the High RED group habituated to the CS+ faster than the Low RED group. However, this explanation lacks a theoretical foundation. Indeed, obese children (Temple, Giacomelli, Kent, Roemmich, & Epstein, 2007) and adults (Epstein, Paluch, & Coleman, 1996) habituate *slower* to food cues than healthy weight individuals (Epstein, Temple, & Bouton, 2009). As RED scores and obesity are highly correlated (Epel et al., 2014), we feel it is unlikely that the High RED group simply habituated faster to the CS+. Third, the "Proactive" account assumes that the High RED group has impaired reactive inhibitory control. However, this has not been directly tested or verified. Future studies should examine how High and Low RED individuals differ in a basic stop-signal task, which is better suited to capture reactive inhibition. Overall, better testing the proactive control

account, especially the possibility that proactive response suppression is used, requires neurophysiological measures to more directly assess motor suppression prior to trial onset.

An extant question is why the slowing of the goCS+ reaction time (for High vs. Low RED) was not evident for overweight/obese versus healthy weight individuals, given that obesity relates to diminished reactive inhibitory control. One possible explanation is that control over response provocation by a Pavlovian cue fits the RED scale measure much better than BMI. We suppose that further exploration into how the RED scale relates to response suppression and other measures of self-control will be of great value.

Conclusions

We set out to better understand if and how appetitive motivation and response control are altered in individuals with varying weights and reward sensitivity. We found that individuals with high reward eating drive were less provoked by the motivating CS+ stimulus as the task progressed. We propose that the reduced provocation is due to individuals with a high reward eating drive adopting a more proactive strategy throughout the course of the experiment to help mitigate inappropriate provocation on “dangerous” nogoCS+ trials. This would be particularly important if individuals with high reward eating drive also have deficient reactive control mechanisms, which should be tested in future studies.

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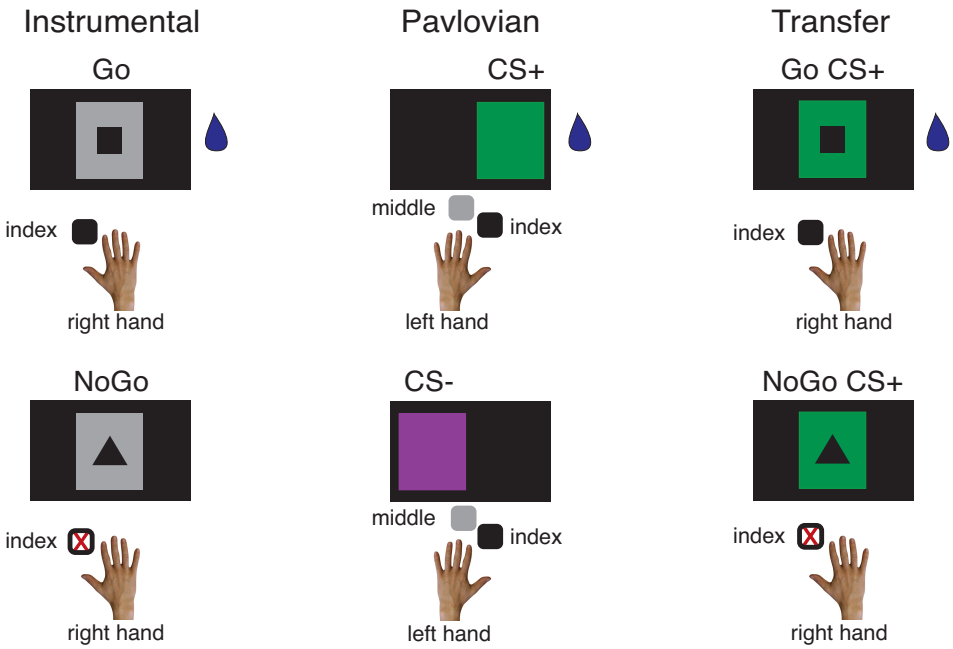

Figure 3.1: Go-nogo/Pavlovian-to-instrumental transfer task. (A) In the Instrumental phase, participants continuously pressed with the right index finger to obtain juice on go (square) trials. Juice delivery was based on a variable ratio reward schedule. On nogo (triangle) trials, no press was to be 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.

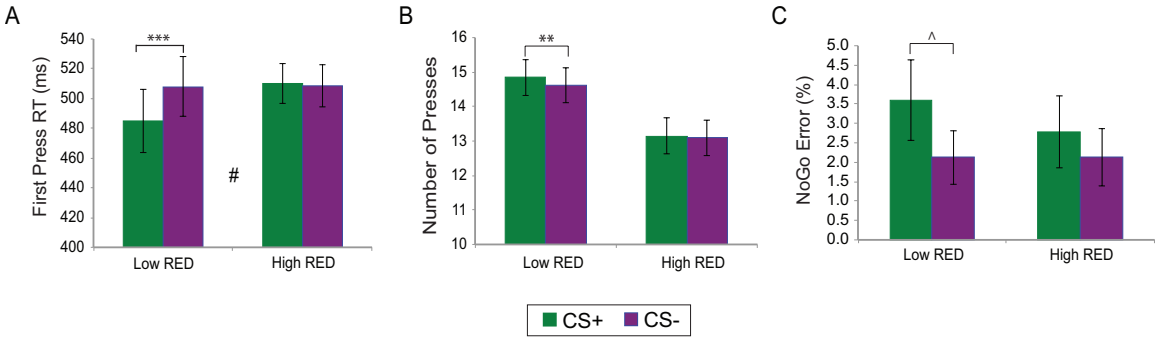

Figure 3.2: PIT results for High and Low RED groups. (A) The Low RED group showed significantly faster first press reaction times (RTs) for the CS+ versus the CS- stimulus (i.e. a "PIT effect"). In contast, the High RED group showed no provocation by the CS+ stimulus, resulting in an interaction. (B) The Low RED group made significantly more presses for the CS+ versus the CS- stimulus, while the High RED group did not show a difference. (C) The Low RED group showed a marginally significant difference in the nogo error rate for the CS+ versus the CS-, while the High RED group showed no difference. Error bars represent the SEM across participants. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$, #$p < 0.05$ for Group x Stimulus interaction.

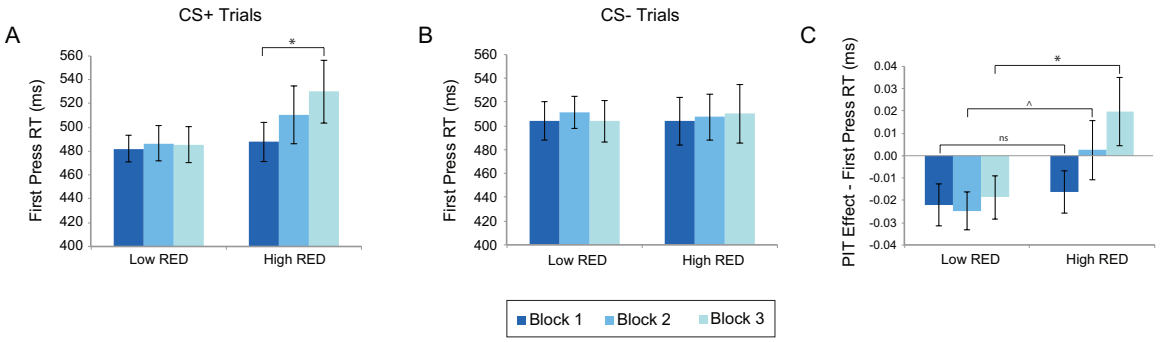

Figure 3.3: The reaction time (RT) PIT effect across blocks. (A) For CS+ trials, the Low RED group showed no change across blocks. Meanwhile, the CS+ RT in the High RED group started out roughly the same as the CS- RT, but became progressively slower across the three blocks in a monotonic fashion. (B) For CS- trials, there was no change across blocks for the High or Low RED groups. (C) The group difference (High RED versus Low RED) in the RT PIT effect (CS+ minus CS-) started to emerge in block 2 and was significantly different in block 3. Error bars represent the SEM across participants. *$p < 0.05$, ^$p < 0.1$.

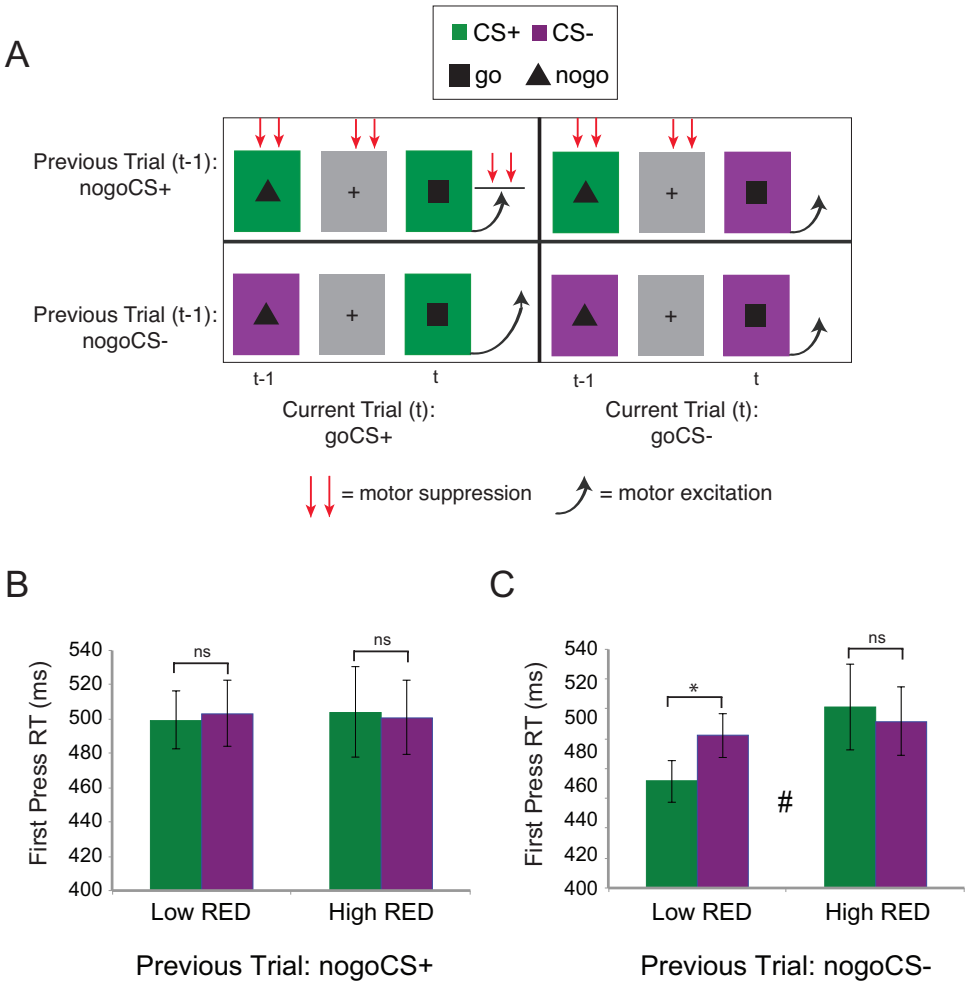

Figure 3.4: A test of the proactive control account. (A) A hypothesized model of proactive control in the go-nogo/PIT task (reprinted with permission from Freeman et al., 2015). After nogoCS+ trials, proactive suppression is engaged to prevent potential provocation on the next trial. If a CS+ occurs, its normal energization is mitigated; whereas, if a CS- occurs, the proactive suppression is released, since CS- trials (unlike CS+ trials) present little "danger" of motivating an action when it is inappropriate to do so. (B) Following nogoCS+ trials, both High and Low RED groups show a reduced influence from the CS+ stimulus—consistent with Freeman et al. (2015). However, following nogoCS- trials, the Low RED group shows CS+ provocation, while it continues to be mitigated in the High RED group. Error bars represent the SEM across participants. *$p < 0.05$, #$p < 0.05$ for Group x Stimulus interaction.

Chapter 3, in full, is currently being prepared for submission for publication of the material. Freeman, Scott M.; Monreal, Teresa; Mello, Melissa; Huh, Paulina, Aron, Adam R.; Boutelle, Kerri, N. The dissertation author was the primary investigator and author of this paper.

CHAPTER 4

Withholding a reward-driven action: Studies of the rise and fall of motor activation and the effect of cognitive depletion

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As it appears in

Journal of Cognitive Neuroscience

2016

Volume 28, Issue 2, Pages 237-251

Withholding a Reward-driven Action: Studies of the Rise and Fall of Motor Activation and the Effect of Cognitive Depletion

Scott M. Freeman and Adam R. Aron

Abstract

■ Controlling an inappropriate response tendency in the face of a reward-predicting stimulus likely depends on the strength of the reward-driven activation, the strength of a putative top–down control process, and their relative timing. We developed a rewarded go/no-go paradigm to investigate such dynamics. Participants made rapid responses (on go trials) to high versus low reward-predicting stimuli and sometimes had to withhold responding (on no-go trials) in the face of the same stimuli. Behaviorally, for high versus low reward stimuli, responses were faster on go trials, and there were more errors of commission on no-go trials. We used single-pulse TMS to map out the corticospinal excitability dynamics, especially on no-go trials where control is needed. For successful no-go trials, there was an early rise in motor activation that was then sharply reduced beneath baseline. This activation–reduction pattern was more pronounced for high- versus low-reward trials and in individuals with greater motivational drive for reward. A follow-on experiment showed that, when participants were fatigued by an effortful task, they made more errors on no-go trials for high versus low reward stimuli. Together, these studies show that, when a response is inappropriate, reward-predicting stimuli induce early motor activation, followed by a top–down effortful control process (which we interpret as response suppression) that depends on the strength of the preceding activation. Our findings provide novel information about the activation–suppression dynamics during control over reward-driven actions, and they illustrate how fatigue or depletion leads to control failures in the face of reward. ■

INTRODUCTION

One way that inappropriate action tendencies are controlled is via response suppression. In the laboratory, action tendencies are typically induced by creating or capitalizing on a strong relationship between a stimulus and a particular response (e.g., an arrow pointing right signals a right-hand response in the stop-signal task; Logan, 1994). Although these tasks have yielded insights into how inappropriate action tendencies are controlled, including neural circuits, motor dynamics, and factors that influence control, their relevance to daily life is limited (for reviews on response suppression, see Bari & Robbins, 2013; Ridderinkhof, Forstmann, Wylie, Burle, & van den Wildenberg, 2011; Stinear, Coxon, & Byblow, 2009; Aron, 2007). This is because, unlike the action provocations in these "cold" cognitive psychology tasks, real-world provocations are often driven by the reward-predicting properties of a stimulus (e.g., a tasty food).

In an effort to extend response suppression research to more real-world situations, we recently developed a behavioral paradigm that requires control in the face of motivationally driven provocations (Freeman, Alvernaz, Tonnesen, Linderman, & Aron, 2015; Freeman, Razhas, & Aron, 2014). In this paradigm, participants were either permitted to respond for a small juice reward (go trials) or not permitted to respond (no-go trials), both in the face of a task-irrelevant stimulus that was earlier associated with juice via Pavlovian conditioning. This led participants, on go trials, to respond more quickly and, on no-go trials, to make more errors of inappropriate responding. For the same task, we used single-pulse TMS (spTMS) over primary motor cortex to measure motor system activity. We showed that, on go trials, the stimulus associated with juice (relative to a stimulus that was not associated with juice) increased motor excitability at 250 msec, whereas on successful no-go trials, there was a beneath-baseline reduction at the same time point. We interpreted this reduction as evidence for a response suppression process that helped mitigate the motivationally triggered activation, yielding an activation–suppression dynamic. However, because motor excitability was only measured at a single time point, those studies did not reveal the finer-grained dynamics of the predicted motor activation and motor reduction processes—how fast the activation appears, how high it reaches, when the control kicks in, and how long it lasts. Moreover, without a picture of the dynamics, those studies could not firmly show that the motor reduction was because of a control process that relates to the strength of the preceding activation. In those studies, TMS was limited to a single time point because of the waning influence of the Pavlovian stimulus

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Journal of Cognitive Neuroscience 28:2, pp. 237–251
doi:10.1162/jocn_a_00893

from satiation over time (thus limiting trial numbers). Here, we sought to capture the putative activation–suppression dynamics using a new paradigm.

Now, rather than using Pavlovian-conditioned stimuli associated with juice, we used stimuli that predicted potential monetary rewards on a given trial. On go trials, participants made instrumental responses to obtain a reward in points (later converted to money). The number of potential points on a given trial was indicated by a colored rectangle (one color: high reward, the other: low reward) that was placed behind the go/no-go cue. On no-go trials, participants were required to withhold their pressing, despite the potential provocation induced by the reward stimulus. Because the reward stimulus was now task relevant and because it entailed monetary reward, there were no restrictions on trial numbers. Accordingly, TMS pulses were delivered at 100, 150, 200, and 250 msec after stimulus onset on different trials. We tested the hypothesis that the reward-predicting stimuli would evoke an early rise in motor excitability on both go and no-go trials and that this reward-driven activation would be immediately followed by a sharp reduction in motor excitability on no-go trials. We also hypothesized that, on no-go trials, the high reward stimulus would show a steeper early activation, and we were interested to examine if this sharper rise would be accompanied by a steeper subsequent reduction—which could reflect a more effortful control process that helps mitigate the increased activation. An alternative possibility is that a similar amount of control would be exerted for high- and low-reward trials, which predicts parallel reduction slopes after a greater initial activation for high-reward trials. In a second study, we tested the idea that the reduction phase reflects top–down control over the activation. We did this by first engaging the participants in an effortful task, which should "deplete" top–down resources; we then examined their ability to withhold responding on high- versus low-reward no-go trials.

EXPERIMENT 1

Methods

Participants

There were 30 participants (16 women; mean age = 20.73 years, *SD* = 2.7 years; all right-handed). Two were excluded for having oversaturated motor evoked potentials (MEPs; i.e., MEPs > 2 mV), and two were excluded because of technical malfunctions with the TMS equipment. Thus, all analyses were run on 26 participants, who provided informed consent and passed TMS safety screening.

Task and Procedure

Each participant sat in front of an iMac (Apple, Inc., Cupertino, CA) with a 20-in. monitor (60-Hz refresh rate). On each trial, participants saw either a black triangle or a black square in the center of the screen for 1.75 sec (Figure 1A). Participants were instructed to respond to one of the shapes (go cue) and to withhold responding to the other shape (no-go cue). Go and no-go cues were equiprobable (i.e., 50/50), and the shapes were counterbalanced across participants.

Upon presentation of the go cue, participants could continuously press a button with their right index finger to obtain points, which they were told would translate into money at the end of the experiment. Presses were to be made only during the 1.75-sec duration of the go trial, and participants were instructed to stop pressing once the go cue disappeared. Points were delivered on a variable ratio reward schedule. For the first block (designated as the "learning block"), the required number of presses ranged from four to nine presses based on a uniform distribution. After the learning block, the range was adjusted based on the participant's mean number of presses (rounded to the nearest integer) during the learning block. To maximize motivational drive for reward, the range was adjusted such that the participant could obtain a reward on most (i.e., >50%) but not all go trials. Thus, a mean press rate of 5 yielded a range of 2–7, a mean press rate of 6 yielded a range of 3–8, and so on. The average proportion of rewarded go trials was 0.64 (*SD* = 0.13) across participants. Information regarding the number of presses required for reward was not disclosed to the participants, although they were informed that the required number of presses would vary across trials. If the button was pressed enough times on a given trial, the amount of points earned was displayed at the center of the screen (e.g., "+50"; Figure 1A). If the button was not pressed enough times, a fixation cross appeared, and the intertrial interval (ITI) period began.

The number of possible points to be earned on a given trial was indicated by a large, colored (blue or yellow) rectangle that surrounded the go cue and was presented simultaneously. If enough presses were made on a high-reward go trial, participants received between 50 and 100 points (in increments of 10, chosen randomly). For low-reward go trials, participants received between 1 and 5 points (in increments of 1, chosen randomly). Participants were informed before the experiment that approximately 1000 points yielded $1. High- and low-reward colors were counterbalanced across participants.

Upon presentation of the no-go cue, participants were required to withhold responding. If a press was mistakenly made on a no-go trial, a red error message reading, "Do Not Press the Button!", was flashed for 1 sec. The no-go cue was also surrounded by a blue or yellow rectangle (which signals reward on go trials), thereby manipulating participants' motivational drive even while they were required to withhold a response (Figure 1A).

All trials were separated by a fixation cross for a variable ITI of 1.75–3 sec (in increments of 0.25 sec, chosen randomly). Go and no-go cues were presented pseudorandomly such that no more than four go or no-go cues

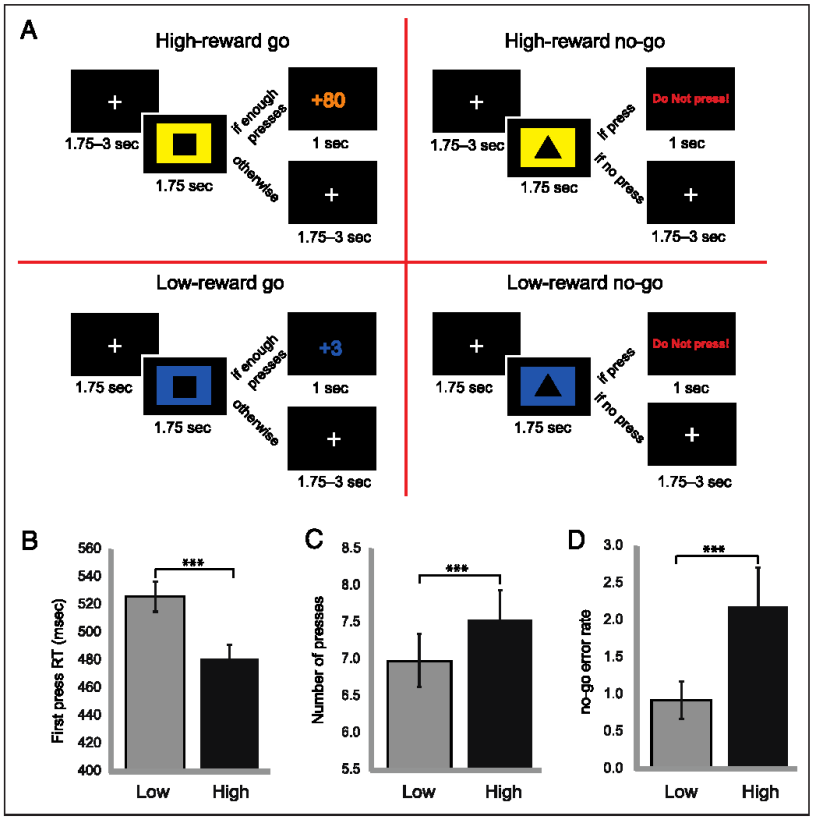

Figure 1. Rewarded go/no-go task and behavior. On go trials (left), continuous presses were made in effort to receive points (later converted to money). If enough presses were made on a given trial, the earned points were displayed to the participant; otherwise, no points were displayed, and the next trial began. The amount of potential points to be earned on a given trial was indicated by the background color. One color (shown as yellow here) was associated with substantially higher point rewards than the other color (shown as blue here). On no-go trials (right), responding was to be withheld; else, a red error message appeared. Go and no-go trials were equiprobable. (B) On go trials, the first press RT was significantly faster for high- compared with low-reward trials. (C) On go trials, more presses were made for high- compared with low-reward trials. (D) On no-go trials, the error rate was significantly greater for high- compared with low-reward trials. This indicates that the high-reward background stimulus provoked responding on both go and no-go trials. Error bars represent *SEM* across participants. ***$p < .001$.

could occur in succession. There were 14 total blocks with 52 trials in each block, yielding 728 total trials. At the end of each block, the number of cumulative points the participant had earned appeared at the top of the screen. At the end of the experiment, the total number of points earned was divided by 1000 and then converted to a rounded dollar amount. The mode for the total money earned across participants was $9. After the experiment concluded, all participants completed the Barratt Impulsivity Scale (BIS-11) questionnaire (Patton, 1995).

TMS

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 muscle of the right hand (corresponding to the task-relevant index finger) 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. The angle of the coil was approximately 45° from the central sulcus. We measured resting motor threshold, defined as the minimum stimulation intensity required to induce 0.1-mV peak-to-peak amplitude MEP in 5 of 10 consecutive stimulations (Rossini et al., 1994). Next, starting at resting motor threshold, 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 ensured that the test stimulus intensity was on the ascending limb of the individual's stimulus–response curve, so that both increases and decreases in corticospinal excitability could be detected (Devanne, Lavoie, & Capaday, 1997). This was the intensity used during the experiment proper (mean intensity across participants was 44.7% stimulator output, $SD = 8.16\%$). To measure the dynamics of corticospinal excitability across time, there were four pulse times after stimulus onset (100, 150, 200, and 250 msec),

yielding 42 trials per condition at each time point. There was also one pulse time 500 msec before stimulus onset to provide a baseline measure (56 trials). To optimize EMG over the first dorsal interosseous muscle, the right index finger moved inward to press a vertical key.

Behavioral Analysis

We compared high- and low-reward trials using three dependent measures: (1) the median RT to the first press on go trials (henceforth called first press RT), (2) the mean number of presses during the 1.75-sec response interval, and (3) the percentage of commission errors on no-go trials. As the first block was considered a "learning block" (where participants learned the color–reward associations), these trials were excluded from all analyses. Trials were also excluded if first press RT was less than 100 msec or if a response was not made on a go trial. Differences between high- and low-reward conditions were evaluated using two-tailed, paired t tests.

EMG Analysis

Preprocessing and normalization. An EMG sweep started 200 msec before stimulation. MEPs were identified from the EMG using in-house software developed in MATLAB (The MathWorks, Natick, MA). Trials were excluded if the root mean square EMG in the 100 msec before the TMS pulse was greater than 0.01 mV or if the MEP was less than 0.05 mV. We also excluded trials if the amplitude maxed out at $+1$ or -1 mV, because we used a CED MICRO 1401 system that has a cutoff at 2 mV (range of $+1$ to -1 mV). Thus, we could not be sure of the true MEP amplitude when it exceeded 2 mV (e.g., 2.1 and 4 mV). For this reason, we elected to exclude such MEPs that "maxed out," as we feel that this provides the most accurate version of the MEP data set. Median peak-to-peak amplitudes of MEPs were calculated for all conditions at each time point. Then, the median MEP for each condition was divided (i.e., normalized) by the median MEP of the baseline trials (i.e., the time point at 500 msec before stimulus onset). An examination of the normalized root mean square values for the 100-msec time window before the TMS pulse showed no significant main effects or interactions (all $ps > .05$), demonstrating that the MEP patterns described below were not contaminated by differences in the pre-TMS period.

Go and no-go dynamics. To provide a detailed picture of the dynamics, we conducted several analyses. First, we separately evaluated go and no-go trials using ANOVAs with Reward (high, low) and Pulse time (100, 150, 200, 250 msec) as factors. For all analyses, we excluded no-go trials where a press was made (commission error). All go trials were analyzed, regardless of whether enough presses were made to earn points on the trial. Planned comparisons for high versus low reward were made at each of the four time points using paired t tests with an alpha value set at .05. Because of the strong prediction of larger MEPs for high versus low reward on go trials, one-tailed t tests were used for this analysis, whereas two-tailed t tests were used for the no-go analysis (because the timing could not be predicted a priori). Unless otherwise specified, all reported p values were corrected for four comparisons using the Holm–Bonferroni procedure.

Percent change across time points on no-go trials. To better capture the change across time for no-go trials, we calculated the percent change of the "activation phase" (i.e., where MEPs were predicted to increase across time, reflecting response prepotency) and the "reduction phase" (i.e., where MEPs were predicted to decrease across time, likely reflecting response suppression). We entered the percent change values into a repeated-measures ANOVA with Reward (high, low) and Phase (activation, reduction) as factors. We then used two-tailed, one-sample t tests to examine differences between each condition and a value of zero (representing no change). Pairwise comparisons across conditions were then made using two-tailed, paired t tests. Unless otherwise specified, all reported p values in this analysis were corrected for eight comparisons using the Holm–Bonferroni procedure.

Relationship between reward-based activation and reward-based reduction on no-go trials. We were interested in examining the relationship between motor excitability during the (predicted) activation and reduction phases, particularly as a function of the reward value. Thus, in each participant, we calculated "reward-based" (high minus low reward) difference scores for each phase. Specifically, we subtracted the percent change for high reward from the percent change for low reward in the activation and reduction phases. A Pearson's correlation was then used to test the relationship between participants' reward-based activation and their reward-based reduction.

Relationship between no-go dynamics and error rates. We postulated that the motor dynamics on no-go trials would relate to participants' self-control failures. We therefore examined how the activation, the reduction, and the activation–reduction processes together related to participants' overall error rates on no-go trials (including high- and low-reward trials). To quantify participants' activation and reduction levels, we computed an average score of percent change for the activation and reduction phases separately and correlated these measures with participants' overall no-go error rates using Pearson's correlations. We also correlated their no-go error rates with a composite measure of motor activity in both the activation and reduction phases—henceforth called the "activation–reduction index." To calculate the activation–reduction index, we first summed the activation and reduction phases for high- and low-reward trials

separately. We then took the average of these two scores to generate an index that reflects both phases and reward values. In essence, this measure provides an index of the strength of the reduction process when taking into account the preceding activation. A Pearson's correlation was then used to test the relationship between participants' overall error rates and the activation–reduction index.

Go and no-go dynamics for fast and slow RT groups. In addition to characterizing the overall dynamics, we reasoned that the motor dynamics in a reward task might depend on participants' basic motivational drive for reward. To examine this, we conducted a median split on the 26 participants based on their RTs, which we used as a behavioral index of motivational drive for reward (faster RT corresponds to higher motivation for reward; Avila & Lin, 2014; Clithero, Reeck, Carter, Smith, & Huettel, 2011). Specifically, we computed the average of the median high-reward RT and the median low-reward RT and took this average as the behavioral index of motivational drive for reward. We then conducted the same dynamics analyses as above for both fast and slow RT groups. Unless otherwise specified, all reported p values were corrected using the Holm–Bonferroni procedure.

Relationship between trait impulsivity and reward-based MEP differences. We acquired answers to a single questionnaire—the BIS-11—to explore a possible relationship between trait impulsivity and sensitivity to reward. We correlated participants' overall BIS-11 scores with their reward-based (high-minus-low difference score) RT, no-go errors, no-go activation phase (percent change from 100 to 150 msec), and the peak activation point on no-go trials (at 150 msec).

Results

Behavior

On go trials, first press RTs were significantly faster for high reward (M = 480.8 msec, SD = 51.4 msec) versus low reward (M = 525.5 msec, SD = 55.4 msec), $t(25)$ = 7.3, $p < .001$ (Figure 1B), showing that the action was invigorated. Participants also made more presses on high-reward (M = 7.55, SD = 2) versus low-reward (M = 6.99, SD = 1.8) trials during the 1.75-sec interval, $t(25)$ = 6.2, $p < .001$ (Figure 1C). On no-go trials, there was a higher percentage of commission errors for high reward (M = 2.2%, SD = 2.7%) versus low reward (M = 0.93%, SD = 1.3%), $t(25)$ = 3.6, p = .001 (Figure 1D), suggesting that the action was also invigorated on no-go trials, which might make it more difficult to withhold. It is worth noting that, although there was a differential increase in no-go error rates for high- versus low-reward trials, no-go error rates for both trial types were low. Thus, our MEP analysis focused solely on successful no-go trials, as there were insufficient trial numbers to analyze unsuccessful no-go trials.

MEPs

This study aimed to examine the dynamics at 100, 150, 200, and 250 msec after high and low reward stimuli on go and no-go trials separately. We were particularly interested in examining the putative activation–reduction dynamics on no-go trials and how this was different for high versus low reward stimuli.

Go and no-go dynamics. For go trials, there was a significant main effect of Reward ($F(1, 25) = 5.87, p = .023$) with MEPs for high reward greater than low reward. There was also a significant Reward × Pulse time interaction ($F(3, 75) = 2.97, p = .037$). For high-reward go trials, there was a significant linear increase in motor excitability across the overall mean values in the four time points ($r_3 = 0.95, p = .026$); whereas, for low-reward go trials, motor excitability decreased from 100–200 msec, followed by an increase from 200–250 msec (Figure 2A). Follow-up t tests showed significantly elevated MEPs for the high reward stimulus at 150 msec ($t(25) = 2.41, p = .047$) and marginally elevated MEPs at 200 msec ($t(25) = 2.16, p = .06$; Figure 2A). This shows that very early motor activity is influenced by the value of a reward-predicting stimulus, which is consistent with several previous studies (Mooshagian, Keisler, Zimmermann, Schweickert, & Wassermann, 2015; Suzuki et al., 2014; Klein, Olivier, & Duque, 2012; Klein-Flügge & Bestmann, 2012).[1]

For no-go trials, there was a main effect of Pulse time ($F(3, 75) = 16.09, p < .001$), where an initial increase in MEPs was followed by a sharp decrease (Figure 2B). The high-reward trials evidenced a greater early elevation in MEPs (at the 150-msec time point) compared with low-reward trials (1.11 vs. 1.03 mV), although the difference was not significant ($t(25) = 1.1$, *ns*; Figure 2B). After the initial activation, there was a steep, beneath-baseline reduction in motor excitability for both high- and low-reward trials (250-msec time point vs. baseline: $p < .001$ for high and low reward). Thus, as predicted, no-go trials exhibited a pattern where an initial activation was followed by a steep reduction in motor excitability. We now explore the activation and reduction dynamics in more detail.

Percent change across time points on no-go trials. The activation phase on no-go trials evidently occurred from 100 to 150 msec after stimulus onset, whereas the reduction phase occurred from 150 to 250 msec (Figure 2B). To quantify the MEP change across time, we calculated the percent change from 100 to 150 msec (constituting the activation phase) as well as the percent change from 150 to 250 msec (constituting the reduction phase) for the high- and low-reward stimuli. In the activation phase, there was some evidence for an early increase in motor excitability for the high ($t(25) = 2.3; p = .03$, uncorrected;

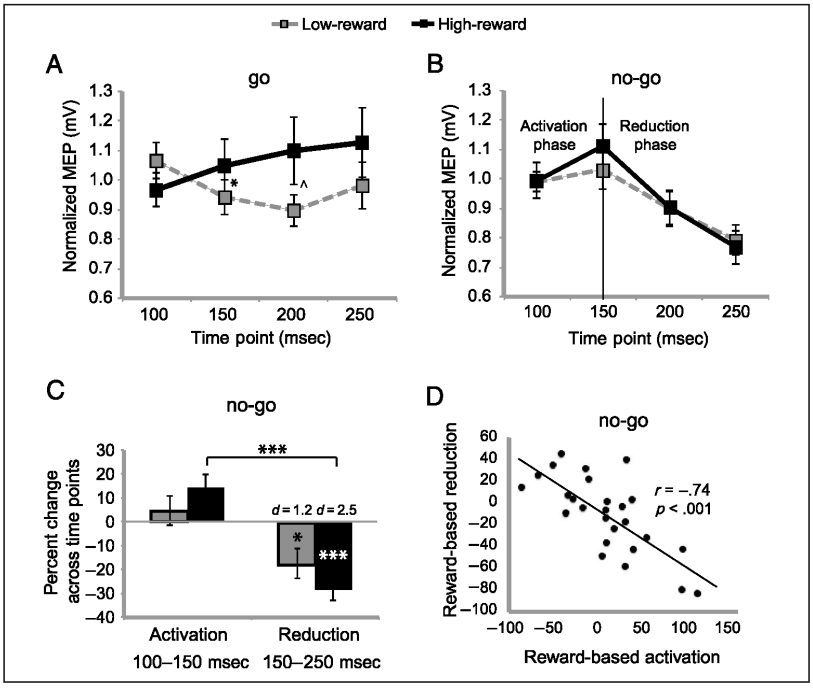

Figure 2. TMS dynamics in Experiment 1. (A) High-reward go trials showed a linear increase in motor excitability across the four time points. Low-reward go trials showed an initial decrease in motor excitability (from 100 to 200 msec), followed by an increase from 200 to 250 msec. (B) On no-go trials, high and low reward showed an initial increase in motor excitability from 100 to 150 msec (activation phase), followed by a decrease from 150 to 250 msec (reduction phase). (C) On no-go trials, the percent change for the reduction phase was twice as strong (measured via effect size) for high- versus low-reward trials, and only high-reward trials showed a significant difference between percent change in the activation and reduction phases. (D) On no-go trials, greater reward-based (i.e., high minus low reward) activation was related to a greater reward-based reduction. Error bars represent *SEM* across participants. ^$p < .06$, *$p < .05$, ***$p < .001$. All p values are adjusted according to Holm–Bonferroni correction.

$d = 0.45$) but not the low ($t(25) < 1$; *ns*, uncorrected; $d = 0.15$) reward stimulus. In the reduction phase, both the high and low reward stimuli showed significant decreases in motor excitability ($t(25) = 6.31, p < .001$ and $t(25) = 3.18, p = .03$, respectively); however, the effect size was more than twice as large for the high reward stimulus (high reward: $d = 2.5$, low reward: $d = 1.2$; Figure 2C). Moreover, only the high reward stimulus showed a difference in the percent change values between the activation and reduction phases (high reward: $t(25) = 4.96, p < .001$; low reward: $t(25) = 2.18$, *ns*; Figure 2C). Taken together, these results support the hypothesized activation–reduction dynamics and also suggest that a larger initial increase in motor excitability (induced by the high reward stimulus) influences the dynamics of the reduction phase. This is in contrast to the possibility that the activation and reduction processes are independent of one another, which would result in similar reduction slopes regardless of differences in initial activation.

Relationship between reward-based activation and reward-based reduction on no-go trials. We next asked if, across participants, the reward-based activation (percent change in MEPs for high minus low reward from 100 to 150 msec) correlated with the reward-based reduction (percent change in MEPs for high minus low reward from 150 to 250 msec). There was a strong negative correlation ($r_{25} = -.74, p < .001$), such that participants who showed stronger reward-based activation also showed a stronger reward-based reduction (Figure 2D). For exploratory purposes, we also tested the relationship between the activation and reduction phases for the low- and high-reward no-go trials separately. For low-reward trials, there was a significant correlation between the activation and reduction processes ($r_{25} = -.52, p = .006$). For high-reward trials, the relationship between the activation and reduction processes did not reach significance ($r_{25} = -.32, p = .11$). However, as the results were strongly influenced by one significant outlier (Mahalanobis distance > 3), the relationship was significant with a nonparametric Spearman's test ($\rho = -0.49, p = .01$) and when the outlier was removed from the analysis ($r_{24} = -.43$, $p = .03$). Together, these results show that the degree of reduction on no-go trials is influenced by the strength of the preceding activation. This could be explained by mere passive decay (what rises higher has further to fall) or by

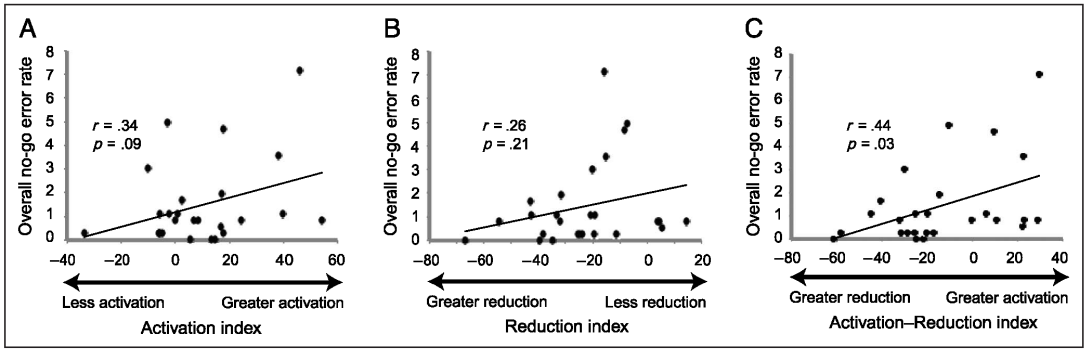

Figure 3. Relationship between the no-go error rate and the different phases of no-go trials. (A) Greater activation from 100 to 150 msec was marginally positively correlated with the no-go error rate. (B) Greater reduction from 150 to 250 msec was positively (but nonsignificantly) correlated with the no-go error rate. (C) The activation–reduction index on no-go trials (a composite measure of the activation and reduction phases) showed a significant positive correlation with the no-go error rate.

a top–down control process. This distinction is tested in Experiment 2.

Relationship between no-go dynamics and error rates. We next examined how the activation, the reduction, and the activation–reduction processes together (reflected in the activation–reduction index) related to participants' self-control failures. Results showed that neither the activation nor reduction processes significantly correlated with participants' overall no-go error rates (activation phase: $r_{25} = .34$, $p = .09$; reduction phase: $r_{25} = .26$, $p = .21$). However, there was a significant correlation between the activation–reduction index and no-go error rates ($r_{25} = .44$, $p = .02$; Figure 3A–C). Specifically, those people who showed a relatively larger increase in the activation phase compared with the decrease in the reduction phase made more errors on no-go trials.

Go and no-go dynamics for fast and slow RT groups. The strength of response activation in a reward task such as this likely depends on the participant's basic level of motivational drive for reward. We therefore split participants

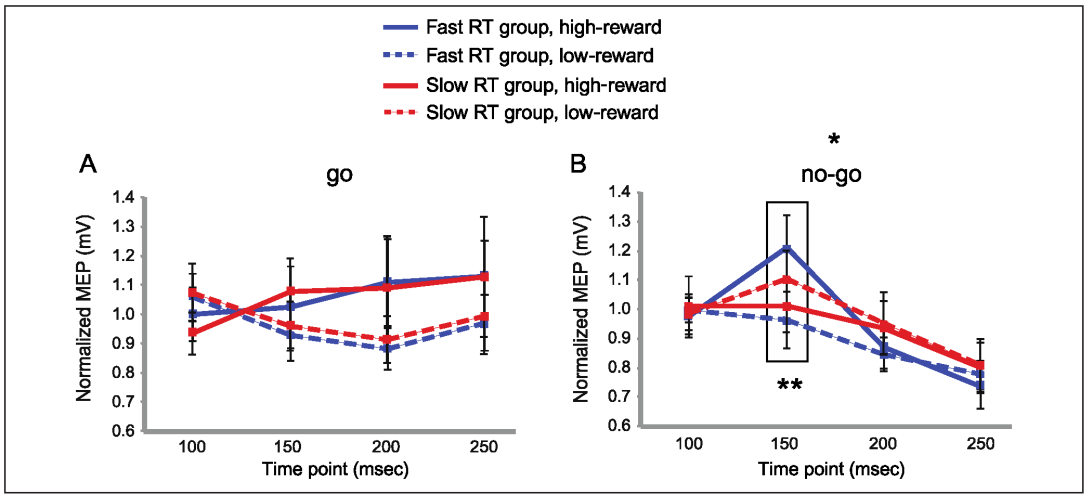

Figure 4. TMS dynamics based on fast and slow RT groups in Experiment 1. (A) Go trial dynamics. High-reward go trials showed an increase in motor excitability across all four time points, whereas low-reward go trials showed a decrease from 100 to 200 msec, followed by an increase from 200 to 250 msec. High- and low-reward go trials in the slow RT group largely resembled that of the fast RT group. (B) High-reward no-go trials in the fast RT group showed an initial steep increase (from 100 to 150 msec), followed by a sharp decrease (from 150 to 250 msec). This pattern was markedly different than low-reward no-go trials, which did not show the initial increase and also a less steep decrease. In contrast to the fast RT group, the slow RT group showed no differences in motor excitability between high- and low-reward no-go trials during the activation and reduction phases. Follow-up analyses showed that group differences in the reward motor dynamics were only in the 150-msec time point. Error bars represent *SEM* across participants. *$p < .05$ for Reward × Pulse time × Group interaction, **$p < .05$ for Reward × Group interaction.

into two groups based on RT on go trials (fast RT vs. slow RT, ostensibly reflecting high and low motivation, respectively). For go trials, a mixed ANOVA with the Reward (high, low) and Pulse time (100, 150, 200, 250 msec) as within-participant factors and Group as a between-participant factor (fast RT, slow RT) revealed a significant main effect of Reward ($F(1, 24) = 5.68, p = .026$), with greater MEPs for high- versus low-reward trials. There was also a significant Reward × Pulse time interaction ($F(3.72) = 2.86, p = .043$; Figure 4A), as was the case in the main analysis with all participants. There was no main effect of or interactions with Group.

For no-go trials, there was a significant main effect of Pulse time ($F(3, 72) = 15.83, p < .001$), in which MEPs began to decrease at 200 msec after stimulus onset. The Reward × Pulse time × Group interaction was also significant ($F(3, 72) = 2.75, p = .049$; Figure 4B). We investigated the triple interaction with separate Reward × Group ANOVAs for each of the four time points, as this would help reveal the specific time points that showed group differences in the reward motor dynamics. We found a significant Reward × Group interaction at only the 150-msec time point ($F(1, 24) = 7.46, p = .01$), in which the fast RT group showed a larger MEP difference between high- and low-reward trials than the slow RT group. This impression was confirmed with t tests that showed a significant high versus low reward difference in the fast RT group ($t(26) = 2.61, p = .02$) but no difference in the slow RT group ($t < 1$, *ns*). It should also be noted that the difference in overall no-go dynamics between the two groups cannot be readily explained by the group difference in overall RT, as this would predict similar patterns of activity, but at different latencies (which was not seen here). Thus, the group that responded more quickly overall on go trials (more putative motivational drive) showed greater sensitivity to the high reward stimulus on no-go trials, particularly at the 150-msec time point.

Percent change across time points on no-go trials for fast and slow RT groups. We now examined the percent change from 100 to 150 and 150 to 250 msec for the

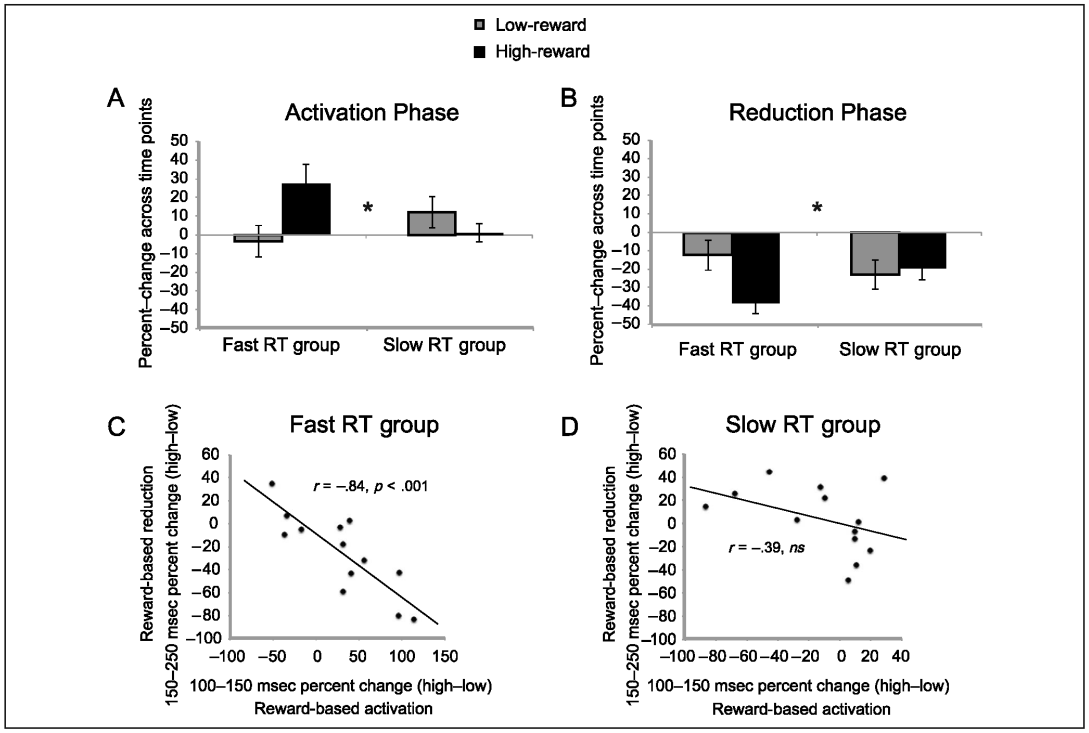

Figure 5. Percent change across time points for fast and slow RT groups on no-go trials, Experiment 1. (A) During the activation phase, the fast and slow RT groups showed different reward motor dynamics, resulting in a significant Group × Reward interaction. Specifically, the fast RT group showed greater sensitivity to the high versus low reward stimulus. (B) During the reduction phase, there was also a significant Group × Reward interaction, where the fast RT group again showed greater sensitivity to the high versus low reward stimulus. (C) The fast RT group showed a significant correlation between the degree of reward-based (i.e., high minus low reward) activation and reward-based reduction. (D) The correlation for the slow RT group did not reach significance; furthermore, a Fisher's r-to-z transformation test revealed that the correlation for the fast RT group was significantly greater than that for the slow RT group. Error bars represent *SEM* across participants. *$p < .05$ for Reward × Group interaction.

activation and reduction phases on no-go trials, for the two groups. An ANOVA with Reward (high, low), Phase (activation, reduction), and Group (fast RT, slow RT) revealed a significant main effect of Phase ($F(1, 24) = 34.01, p < .001$) as well as a Reward × Phase × Group interaction ($F(1, 24) = 6.57, p = .017$). Follow-up ANOVAs for the activation and reduction phases separately showed significant Reward × Group interactions for both phases (activation: $F(1, 24) = 5.62, p = .026$; reduction: $F(1, 24) = 5.41, p = .029$; Figure 5A and B). This is in line with the result above that pinpointed the 150-msec time point as the locus for differential reward motor dynamics across the groups, as it is the only time point that contributes to the percent change in both the activation and reduction phases.

Relationship between reward-based activation and reward-based reduction on no-go trials for fast and slow RT groups. A Pearson's correlation for the fast RT group showed a strong negative correlation between the reward-based activation and reward-based reduction across individuals ($r_{12} = -.84, p < .001$; Figure 5C). This correlation was not present for the slow RT group ($r_{12} = -.39, p = .18$; Figure 5D). A direct comparison of the two correlation coefficients using a Fisher *r*-to-*z* transformation showed that the correlation for the fast RT group was significantly stronger than that of the slow RT group ($Z = 1.82, p = .03$, one tailed). This again indicates that the reduction phase depends on the strength of preceding reward-based activation.

Relationship between trait impulsivity and reward-based MEP differences. Trait impulsivity was only significantly correlated with the peak activation point on no-go trials ($r_{25} = .39, p = .047$, uncorrected for four comparisons), such that higher impulsivity was related to greater sensitivity to the high versus low reward stimulus at the peak point of activation. This suggests that trait impulsivity is related to the reward value in the activation process.

Discussion

TMS was delivered at 100, 150, 200, or 250 msec after a high or low reward stimulus on go and no-go trials to map the dynamics of putative response activation and control. On go trials, the high reward stimulus produced an early motor activation (within 150 msec) that preceded the average RT by almost 350 msec. In contrast, the low reward stimulus showed an initial decrease in motor activation (from 100 to 200 msec), followed by an increase (from 200 to 250 msec),[2] resulting in a significant high versus low reward difference at 150 msec.

On no-go trials, the reward stimuli (especially the high reward stimulus) induced a brief increase in motor excitability (from 100 to 150 msec), followed by a sharp reduction (from 150 to 250 msec) that reached levels far beneath the prestimulus baseline. Notably, those participants with greater activation also showed greater reduction on no-go trials. This suggests that the dynamics of the reduction phase depend on the strength of early reward-driven activation and also suggests that both processes are important when evaluating one's ability to withhold a reward-driven action. In support of this, we found that only a measure that takes into account both the activation and reduction processes together was predictive of participants' overall errors rates on no-go trials. This indicates that higher levels of reward-driven activation are detrimental if a proportionately larger reduction process does not follow. Furthermore, this result highlights the importance of using self-control paradigms that can capture both the provocation and control processes with high temporal resolution.

We also found that individuals with higher motivational drive showed greater sensitivity (i.e., stronger activation and reduction processes) to the high versus low reward stimulus on no-go trials. This indicates that the influence of reward value on the activation–reduction dynamics was highly dependent on participants' motivational drive for reward and also provides further support for the close activation–reduction relationship. Finally, individual difference analyses across all participants revealed that, at the peak point of activation (150 msec), trait impulsivity was positively correlated with the degree of reward-based activation. This indicates that trait impulsivity is related to the reward value in the activation process and, in accordance with our other findings, suggests that greater recruitment of control mechanisms may be required when impulsive individuals view a high reward stimulus. However, this results should be interpreted with caution, as the analysis was not corrected for multiple comparisons.

We interpret the sharp, beneath-baseline reduction in motor excitability on no-go trials as a top–down suppression process that depends on the strength of preceding activation. However, other accounts exist. For example, it is possible that a similar degree of control is instantiated on high- and low-reward no-go trials and that the steeper reduction on high-reward trials is simply a side effect of there being higher initial activation (i.e., further to "fall"). In this case, the reduction phase would reflect a control process that does not necessarily depend on the strength of preceding activation. It is also possible that the reduction phase merely reflects a passive withdrawal of voluntary drive, which could also manifest in reduced motor excitability. In the next experiment, we test these competing accounts using a well-established finding that failures in self-control tend to increase when immediately following a very demanding task (Heatherton & Wagner, 2012; Baumeister & Heatherton, 1996). We reasoned that, if there is top–down response suppression and its strength depends on the preceding activation, then there should be more effortful control recruited on high- compared with low-reward no-go trials. This then predicts that

depleting top–down resources with a demanding earlier task will increase the no-go error rate more for high- versus low-reward trials in our rewarded go/no-go paradigm.

EXPERIMENT 2

Two groups of participants performed the rewarded go/no-go paradigm before and after an extended working memory (WM) task (one group, easy; one group, difficult). We chose a WM manipulation because it allowed us to tax top–down control brain regions, including lateral pFC and parietal cortex (Zanto, Rubens, Thangavel, & Gazzaley, 2011; Owen, McMillan, Laird, & Bullmore, 2005; Braver et al., 2001) that would ostensibly be important for controlling the rapid activation on high-reward no-go trials that we observed in Experiment 1.

On the basis of our hypothesis that top–down response suppression was engaged more on high- versus low-reward no-go trials, we made two specific predictions. First, we predicted that, when top–down resources are depleted (i.e., the high-load group), the change in error rate for high-reward no-go trials would be greater than that for low-reward no-go trials. Second, we predicted that, when top–down resources are not depleted (i.e., the low-load group), there would be no difference between high- and low-reward trials.

Methods

Participants

Forty-two (10 male) participants were tested (mean age = 21.36 years, *SD* = 5.5 years; all right handed). Two participants were excluded because of technical malfunctions. One participant in the low-load group was excluded for having a high-reward error rate of 50%, which was more than 5 *SD*s from the group mean. Thus, all analyses were run on 39 participants, with 19 participants in the low-load group (mean age = 21.5 years, *SD* = 7.7 years) and 20 participants in the high-load group (mean age = 21.15 years, *SD* = 1.9 years). All participants provided institutional review board consent.

Task and Procedure

There were three parts to the procedure (see Figure 6A). In Part 1, all participants completed a task identical in design to the rewarded go/no-go task in Experiment 1 (Figure 1), with the only difference being that there were now four blocks of 48 trials, yielding 208 total trials. As in Experiment 1, the first block was considered a "learning block" and was not included in the analysis. The data from this rewarded go/no-go task served as a baseline measure for each participant to determine the change in the no-go error rate after the WM manipulation.

In Part 2, participants were assigned to either the low- or high-load WM group. For both groups, consonant letters appeared one at a time on the screen (letter duration = 0.75 sec, ITI duration = 1.75 sec). Participants in the low group were instructed to make a response (using their left index finger to make the tasks as orthogonal as possible) as quickly as possible every time the letter "P" appeared on the screen (on trial n). For all other letters, no response was to be made. Participants in the high group were instructed to make a response (using their left index finger) as quickly as possible every time they saw the same letter as presented three letters before (on trial $n-3$). For all other letters, no response was to be made. Participants in this group were told that, to complete the 3-back task, they had to hold three letters at a time in WM and continuously update the three letters with every new letter presentation. For both groups, there were six blocks of 100 analyzable trials (for the 3-back task, the first three trials of each block were excluded), yielding 600 analyzable trials. Participants were given a 20-sec break between each of the six blocks. All participants completed a practice session of 30 trials. In total, Part 2 took approximately 30 minutes for both groups.

In Part 3, participants again completed the rewarded go/no-go task. However, there were now three blocks of 48 trials (yielding 144 total trials), but with no learning block (because the color–reward relationships had already been learned in Part 1). Thus, the number of analyzable trials was identical for Parts 1 and 3.

Data Analysis

The main dependent measure was the change in error rate on no-go trials from before the WM manipulation to after (pre to post). We therefore calculated post-minus-pre difference scores in the error rate for high and low reward in both load groups. To test for pre-to-post changes in error rate, we used one-sample t tests to compare the conditions against a value of zero (representing no pre-to-post change). We also directly compared the pre-to-post change for high versus low reward with paired t tests. On the basis of the strong directional predictions, one-tailed tests were used.

Results

We first verified that the WM manipulation was successful. A two-sample t test showed that performance in the low-load condition was significantly better than in the high-load condition ($t(38) = 8.58$, $p < .001$; Figure 6B). We then verified that, before the WM manipulation, there were no group differences in high- minus low-reward RT or total errors (all ps > 0.2; see Table 1 for behavioral measures). Finally, we verified that there were no pre-to-post changes or group differences for overall RT or number of presses ($t < 1$, *ns*), suggesting that cue processing speed

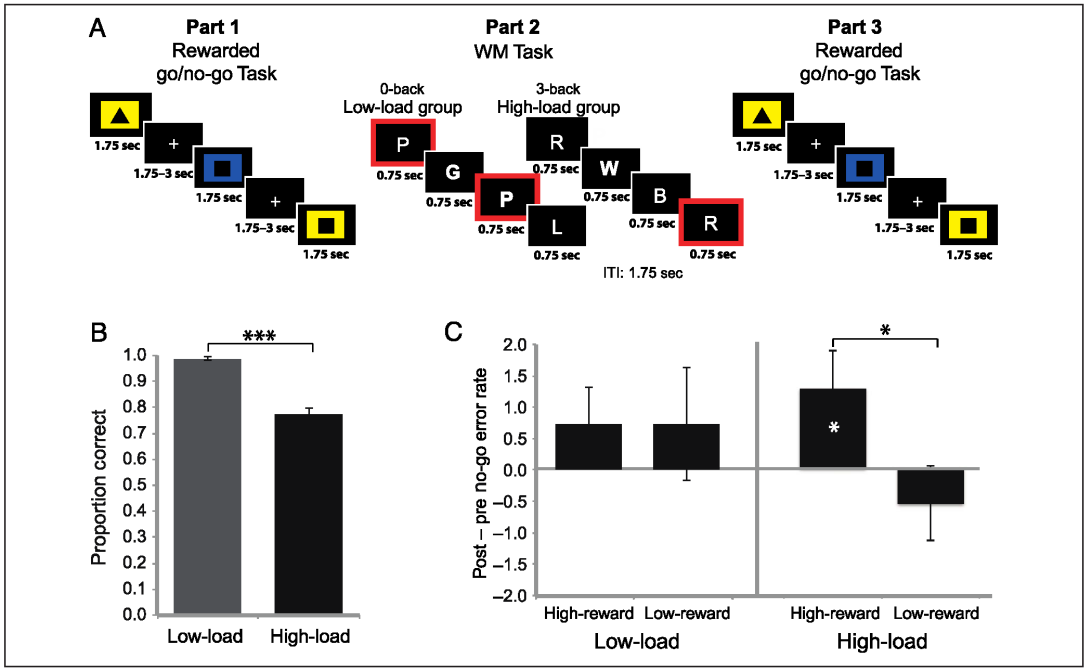

Figure 6. Experiment 2 task design and results. (A) There were three parts in the task. In Part 1, participants completed the rewarded go/no-go task (as in Experiment 1). This provided a baseline measurement for each participant's no-go error rate on high- and low-reward trials. In Part 2, participants either completed a cognitively demanding 3-back WM task (high load) or a less demanding 0-back task (low load). For the 0-back task, they were required to press a button (indicated by a red outline) whenever they saw the letter "P." For the 3-back task, they were required to press a button whenever the current letter matched the letter presented three letters before. In Part 3, participants completed another rewarded go/no-go task to examine the change in error rates on high- and low-reward no-go trials after the WM manipulation. (B) A proportion correct measurement showed that the high-load (3-back) task was significantly more difficult than the low-load (0-back) task. (C) Only high-reward trials in the high-load group showed a significant increase in the error rate after the WM manipulation. This increase was significantly greater than the low-reward trials in the high-load group. The low-load group showed no difference between high- and low-reward no-go trials and no pre–post changes in error rates. Error bars represent *SEM* across participants. *$p < .05$, ***$p < .001$.

and motivational drive were not affected by the WM manipulation.

Our main analysis showed that, in the high-load group, there was a significant pre-to-post increase in error rate for the high ($t(19) = 2.13, p = .02$) but not the low ($t(19) < 1$) reward stimulus and a significant difference between the high and low reward stimuli ($t(18) = 2.29, p = .02$; Figure 6C). For the low-load group, there were no significant pre-to-post changes for either the high or low reward stimulus, nor was there a difference between the two conditions (all $ps > .2$; Figure 6C). A direct comparison between the groups using a mixed ANOVA with load (high, low) as a between-participant factor and reward (high, low) as a within-participant factor showed a trending interaction ($F(1, 37) = 2.1, p = .08$).

Discussion

One group of participants underwent the rewarded go/no-go task, then an easy (low-load) WM task, and then

Table 1. Behavioral Measures for Experiment 2

	Load	*Overall RT (msec)*	*High RT (msec)*	*Low RT (msec)*	*Overall Error Rate*	*High Error Rate*	*Low Error Rate*
Pre	Low	419.3 (62)	406.1 (64)	434.7 (67)	2.56 (2.33)	3.65 (3.47)	1.46 (2.68)
	High	418.4 (40)	408.2 (48)	431.1 (43)	1.60 (2.22)	1.81 (2.89)	1.39 (2.63)
Post	Low	410.6 (63)	393.4 (60)	425.7 (64)	4.93 (3.94)	4.39 (3.38)	2.19 (3.28)
	High	412.2 (43)	398.3 (43)	430.9 (48)	2.92 (4.80)	3.06 (3.92)	0.83 (3.13)

the rewarded go/no-go task again, whereas another group of participants did the same sequence but with a difficult (high-load) WM task. The high-load version was an effortful 3-back WM paradigm that putatively "depletes" cognitive resources commonly involved in top–down control (Chmielewski, Mückschel, Stock, & Beste, 2015; Mitchell, Macrae, & Gilchrist, 2002). In the high-load group, we observed a significant pre-to-post increase in the no-go error rate only for high-reward trials, which was significantly greater than the pre-to-post change for low-reward trials. This was not the case for the low-load group, most likely because top–down resources were not depleted. Ideally, there would also be a significant difference between groups, which was only present here at a trend level. However, the comparison was not between high WM and no intervening task but between high- and low-load WM (which would also be depleting to some extent). Notwithstanding, the increased error rate for high- versus low-reward no-go trials in the high-WM group suggests that greater top–down control is needed on high-reward no-go trials. This, along with the evidence for stable levels of motivation, argues against the possibility that the reduction phase reflects a withdrawal of voluntary drive and is in line with the hypothesis that it reflects a top–down suppression process that is related to the strength of preceding activation.

GENERAL DISCUSSION

Recent studies suggested that motivationally driven action tendencies can be countered by a response suppression mechanism (Freeman et al., 2014, 2015), but they did not reveal the putative activation–suppression dynamics. It was therefore unclear if the motor reduction previously observed on no-go trials was preceded by an early rise in reward-driven motor activation and whether the reduction was directly related to the putative early activation. Here, we employed a rewarded go/no-go paradigm with better characteristics for mapping out the corticospinal dynamics. In Experiment 1, we found that no-go trials showed an initial activation phase (within 150 msec), followed by a sharp reduction phase (within 200 msec) that fell beneath prestimulus baseline levels by 250-msec poststimulus onset. The activation–reduction pattern was more pronounced (i.e., showed a greater magnitude in the slope change) for high- versus low-reward no-go trials, indicating that the reduction phase was related to the degree of preceding activation. In support of the activation–reduction link, there was a strong correlation between the amount of activation and reduction across individuals, suggesting that both processes are important when evaluating one's ability to withhold a reward-driven action. In line with this, we found that a measure that takes into account both the activation and reduction processes together was predictive of participants' overall errors rates on no-go trials. Moreover, subgroup analyses revealed the importance of taking into account individuals' basic motivational drive for reward, as individuals with higher drive showed greater sensitivity (i.e., response activation) toward a high reward stimulus, followed by a steeper reduction slope. We hypothesized that the steeper reduction slope reflects greater top–down suppression. If so, then depleted cognitive resources should increase the no-go error rate more for high- versus low-reward trials, which is what we found in Experiment 2. Thus, our results show that, when it is inappropriate to respond, reward-predicting stimuli still induce an early rise in motor activation that is subsequently controlled. This leads to a reduction of motor excitability well beneath baseline, and the strength of this reduction appears to depend on the strength of the preceding activation. Together, these results suggest that controlling reward-driven responses may critically depend on the tight relationship between the activation and reduction phases and that a weakened reduction process can lead to failures in self-control.

What is the top–down control process that apparently "kicks in" on high-reward no-go trials? One possibility is that it is response suppression, as we have previously postulated. This is consistent with many response control studies that have demonstrated the recruitment of an active suppression mechanism that countermands an action tendency from a prepotent or an already-initiated response, for example, in the stop signal paradigm (Schmidt, Leventhal, Mallet, Chen, & Berke, 2013; Aron, 2007; Aron & Poldrack, 2006). It is also consistent with several stop signal and go/no-go studies that have used spTMS to characterize the timing of the putative response suppression process on stop or no-go trials. In particular, those studies have typically observed response suppression at 140–200 msec after stimulus onset (van den Wildenberg et al., 2010; Stinear et al., 2009; Coxon, Stinear, & Byblow, 2006; Yamanaka et al., 2002; Hoshiyama et al., 1997), which closely mirrors the timing in the current study.

An alternative top–down control process could be attentional modulation. This could direct resources away from the reward stimulus and/or toward the no-go cue (Hickey & Peelen, 2015; Harris, Hare, & Rangel, 2013; Giesbrecht, Woldorff, Song, & Mangun, 2003; Hopfinger, Buonocore, & Mangun, 2000). For example, the study by Harris et al. (2013) found evidence for an early attentional filtering mechanism during the exercise of self-control in the face of appetitive food items. Notably, the attentional filtering mechanism was instantiated 150–200 msec after stimulus onset, which also closely resembles the timing of the reduction phase in the current study. It is therefore possible that, here, the reduction phase actually reflects a reduction in motivational drive after reduced processing (via attentional control) of the reward stimulus. Notwithstanding this possibility, this attention explanation has difficulty accounting for the beneath-baseline reduction we observed. Instead, an attentional filtering of the reward stimulus would more likely cause a reduction in motor excitability to prestimulus onset levels where no stimulus is displayed.

Future studies could more definitively disentangle such mechanisms with functional neuroimaging. For example, a response suppression account predicts the involvement of regions implicated in stopping action, such as the right inferior frontal gyrus, pre-supplementary motor area, and subthalamic nucleus (Chambers, Garavan, & Bellgrove, 2009; Aron, 2007; Aron & Poldrack, 2006; Garavan, Hester, Murphy, Fassbender, & Kelly, 2006). Alternatively, the attentional control account predicts the involvement of regions implicated in downmodulating task-irrelevant distractors, such as the superior frontal cortex, inferior frontal junction, and parietal cortex (Zanto et al., 2011; Giesbrecht et al., 2003; Hopfinger et al., 2000). Ultimately, clarifying the underlying mechanism could help inform when and how control is implemented over reward-driven provocations. In turn, this information could be useful in determining optimal tasks that may be used to train individuals over extended periods in an effort to reduce failures in self-control.

Here, we show that one condition that leads to increased failures in self-control is when a strong activation must be withheld (i.e., on high-reward no-go trials) after top–down resources have been heavily taxed. This result fits with a large literature that finds increased failures in self-control immediately after cognitive resources have been "depleted" in a separate effortful task (often referred to as "ego depletion"; Hagger, Wood, & Stiff, 2010; Baumeister & Heatherton, 1996). To account for these findings, it is thought that self-control draws from a somewhat global, limited resource and that exhausting it reduces the amount (or allocation) of available self-control resources to be deployed in the near future (Baumeister, 2014; Gailliot et al., 2007; Baumeister & Heatherton, 1996). An alternative theory explains the decrement in self-control as a decrease in participants' motivational state during the second task (Inzlicht, Schmeichel, & Macrae, 2014). Our results argue against the motivational account, as we found no pre-to-post changes in participants' motivational drive for reward (measured via RT and number of presses). Moreover, it is unclear why the motivational change would only occur for high-reward no-go trials, as the low-reward no-go trials showed no pre-to-post change. Instead, our results suggest that the reduction phase reflects a top–down control process and that the implementation of top–down control is affected by a demanding WM task.

The current approach has greater ecological validity than typical studies of response control, as we have studied the control over a reward-driven response tendency rather than merely a response tendency that is preestablished or automatic (as in the Simon or Flanker tasks). Yet, our approach is still limited by the fact that the no-go cue is an external signal.[3] In many real-world situations of self-control, there is no cue or signal instructing individuals to withhold an action. Instead, people must often generate the control process in an endogenous manner (there are, however, some real-world situations that are analogous to the current case; for example, the no-go trials in the current study are perhaps analogous to the scenario in which a smoker views a pack of cigarettes that has a large warning message on the front). Although paradigms have been designed to investigate endogenous control (for a review, see Ridderinkhof, van den Wildenberg, & Brass, 2014; Filevich, Kühn, & Haggard, 2012), studying endogenous control poses several challenges. For one thing, withholding a response endogenously is a subjective, decision-based process, which makes it difficult to measure a response inhibition failure. For another, the timing of the activation and control processes is more variable, which could limit the use of techniques such as spTMS to map the dynamics. Future studies will therefore benefit from discovering neural markers that signify both the activation and control processes within a single task, as this will allow a "readout" of their timing and relative strength during endogenous recruitment. A second limitation of the current study is that, from Experiment 2, we could only infer that the increase in errors was because of a change in the reduction phase dynamics. A future study could more definitively establish that this is the case using spTMS with the rewarded go/no-go task after a depletion manipulation. We predict that, whereas the activation phase would show a similar pattern as we observed here, the reduction phase on high-reward trials would show a less steep decrease in motor activity, thereby eroding its relationship with the preceding activation.

In conclusion, we show that, when a reward-driven action was withheld, there was an initial rise in motor activation that was modulated by the value of the reward-predicting stimulus and the individual's motivational drive for reward. Furthermore, the initial activation phase was followed by a steep reduction in motor excitability, with the degree of the reduction corresponding to the strength of preceding activation. This pattern of dynamics, along with the observation that an effortful task apparently depletes the ability to withhold a response in the face of the high reward stimulus, suggests that the control process involved top–down response suppression. Future studies could validate this, which would highlight the importance of using response suppression to control provocations driven by the motivational content of a stimulus. More generally, these dynamics suggest that failures in controlling reward-driven actions may be due to insufficient or depleted response suppression mechanisms that follow a quick rise of reward-driven activation. This may explain why self-control is more difficult and fails more often when following demanding tasks (van der Linden, Frese, & Meijman, 2003; Baumeister, Bratslavsky, Muraven, & Tice, 1998) or consumption of substances (e.g., alcohol; Kähkönen, Wilenius, Nikulin, Ollikainen, & Ilmoniemi, 2003; Moselhy, Georgiou, & Kahn, 2001) that reduce functioning in brain regions involved in top–down control. Specifically, our findings suggest that reduced functioning in top–down control

may lead to a weakened suppression process, contributing to failures in self-control.

Acknowledgments

This work was supported by U.S. National Institutes of Health grant DA026452 and James S. McDonnell Scholar Award 220020375 to A. R. A. and by a National Science Foundation Graduate Research Fellowship to S. M. F. We would also like to thank Dianze Lu for assistance with data collection.

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Notes

1. These early MEP differences between high- and low-reward trials are probably not merely because of faster RTs on high-reward trials for several reasons. First, the MEP differences were, on average, more than 280 msec before the mean high-reward RT. As previous studies have shown that increases in MEP amplitude resulting from voluntary movement initiation generally occur only about 100 msec before the RT (Stinear et al., 2009), this result is likely independent of RT differences. Second, we computed RT difference scores (high minus low reward) for each individual and correlated these with their MEP difference scores (high minus low reward) at the 150- and 200-msec time points. If the high versus low MEP results were merely because of differences in RT, we would expect that participants with a larger behavioral effect (high vs. low) would also show a larger MEP effect (high vs. low). There was no evidence for a significant interparticipant correlation across these difference scores at the 150- or 200-msec time point ($ps > .4$), indicating that the MEP differences were likely not influenced by differences in RT. Finally, the finding of differential MEP activity as a result of differential reward value has been found in several previous studies that have pulsed in a response-locked fashion (e.g., Klein-Flügge & Bestmann, 2012), suggesting that the differences observed here are not because of the stimulus-locked TMS pulses.
2. Whereas the increase in motor excitability for high-reward go trials was in line with our predictions, the initial decrease on low-reward go trials was surprising. One intriguing possibility for the decrease is that making effortful instrumental responses to a low reward stimulus may be somewhat aversive (Talmi, Dayan, Kiebel, Frith, & Dolan, 2009; Hare, O'Doherty, Camerer, Schultz, & Rangel, 2008), which could in turn trigger a quick inhibitory response over the motor system (Verbruggen, Best, Bowditch, Stevens, & McLaren, 2014). This possibility warrants further investigation, particularly in light of the translational implications of establishing a physiological link between stimulus aversion and its influence on triggering motor inhibition (Chiu, Cools, & Aron, 2014).
3. There are also some remaining questions pertaining to the results. For example, it is unclear if the dynamics observed in the current study would resemble the dynamics in the paradigm used in Freeman et al. (2014), where the background stimulus is a task-irrelevant Pavlovian cue that motivates instrumental responding. It is also unclear why the initial reward-based activation process on no-go trials (from 100 to 150 msec) did not more closely match the go trials during the same period. Finally, we are not certain why the fast RT group's greater sensitivity to the high reward stimulus was observed on no-go trials but was not observed on go trials.

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Chapter 4, in full, is a reprint of the material as it appears in *Journal of Cognitive Neuroscience*. Freeman, Scott M.; Aron, Adam, R., 2015. The dissertation author was the primary investigator and author of this paper.

CHAPTER 5

High working memory load increases intracortical inhibition in primary motor cortex and diminishes the motor affordance effect

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As it appears in

Journal of Neuroscience

2016

Volume 36, Issue 20, Pages 5544-5555

5544 • The Journal of Neuroscience, May 18, 2016 • 36(20):5544–5555

Behavioral/Cognitive

High Working Memory Load Increases Intracortical Inhibition in Primary Motor Cortex and Diminishes the Motor Affordance Effect

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Motor affordances occur when the visual properties of an object elicit behaviorally relevant motor representations. Typically, motor affordances only produce subtle effects on response time or on motor activity indexed by neuroimaging/neuroelectrophysiology, but sometimes they can trigger action itself. This is apparent in "utilization behavior," where individuals with frontal cortex damage inappropriately grasp affording objects. This raises the possibility that, in healthy-functioning individuals, frontal cortex helps ensure that irrelevant affordance provocations remain below the threshold for actual movement. In Experiment 1, we tested this "frontal control" hypothesis by "loading" the frontal cortex with an effortful working memory (WM) task (which ostensibly consumes frontal resources) and examined whether this increased EEG measures of motor affordances to irrelevant affording objects. Under low WM load, there were typical motor affordance signatures: an event-related desynchronization in the mu frequency and an increased P300 amplitude for affording (vs nonaffording) objects over centroparietal electrodes. Contrary to our prediction, however, these affordance measures were diminished under high WM load. In Experiment 2, we tested competing mechanisms responsible for the diminished affordance in Experiment 1. We used paired-pulse transcranial magnetic stimulation over primary motor cortex to measure long-interval cortical inhibition. We found greater long-interval cortical inhibition for high versus low load both before and after the affording object, suggesting that a tonic inhibition state in primary motor cortex could prevent the affordance from provoking the motor system. Overall, our results suggest that a high WM load "sets" the motor system into a suppressed state that mitigates motor affordances.

Key words: EEG; GABA; inhibition; motor affordance; working memory

Significance Statement

Is an irrelevant motor affordance more likely to be triggered when you are under low or high cognitive load? We examined this using physiological measures of the motor affordance while working memory load was varied. We observed a typical motor affordance signature when working memory load was low; however, it was abolished when load was high. Further, there was increased intracortical inhibition in primary motor cortex under high working memory load. This suggests that being in a state of high cognitive load "sets" the motor system to be imperturbable to distracting motor influences. This makes a novel link between working memory load and the balance of excitatory/inhibitory activity in the motor cortex and potentially has implications for disorders of impulsivity.

Introduction

Motor affordances occur when the visual properties of an object elicit behaviorally relevant motor representations (Gibson, 1979). For example, viewing a right-facing cup handle activates left hemisphere motor areas (Grafton et al., 1997; Chao and Martin, 2000), resulting in potentiation of the right hand (McBride et al., 2012). Such motor potentiation from affording (vs nonaffording) objects has been observed using a range of methods. These include the following: shorter reaction times (RTs) when the orientation of a handle is compatible with the responding hand (Tucker and Ellis, 1998, 2004), increased BOLD signal in premotor cortex when viewing graspable objects (Grafton et al.,

Received Jan. 26, 2016; revised March 23, 2016; accepted April 9, 2016.
Author contributions: S.M.F. and A.R.A. designed research; S.M.F. performed research; S.I. contributed unpublished reagents/analytic tools; S.M.F. and S.I. analyzed data; S.M.F., S.I., and A.R.A. wrote the paper.
This work was supported by National Institutes of Health Grant DA026452 and James S. McDonnel Scholar Award 220020375 to A.R.A. and National Science Foundation Graduate Research Fellowship to S.M.F. We thank Cathy Stinear for advice with the LICI procedure and Lucia Riggio for the cup stimuli.
The authors declare no competing financial interests.
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DOI:10.1523/JNEUROSCI.0284-16.2016
 0270-6474/16/365544-12$15.00/0

1997; Chao and Martin, 2000), greater motor excitability in the affording effector (measured as motor evoked potentials [MEPs]) (Buccino et al., 2009; Franca et al., 2012), greater mu frequency (7.5–12.5 Hz) event-related desynchronization (ERD) over centroparietal electrodes (Muthukumaraswamy et al., 2004; Proverbio, 2012), and higher amplitude in a late positive event-related potential (ERP) called the P300 (Proverbio et al., 2011; Righi et al., 2014).

Notably, motor affordances appear to occur automatically, as response-compatibility effects are found even when the objects are irrelevant to the task (Ellis and Tucker, 2000; Fischer and Dahl, 2007) and when attention is focused away from the object (Riggio et al., 2008). This automatic motor potentiation could have functional benefits for behavior by facilitating more efficient use of objects that entail action requirements (Handy et al., 2003; Tucker and Ellis, 2004). However, when the affording object is irrelevant to the task, such motor potentiation could be maladaptive by provoking automatic action tendencies that are incongruent with task goals. In line with this, inappropriate reaching and grasping of affording objects have been observed in patients with frontal lobe damage, i.e., so-called "utilization behavior" (Lhermitte, 1983; Shallice et al., 1989; Archibald et al., 2001; Besnard et al., 2010). This raises the possibility that, in healthy-functioning individuals, frontal cortex helps ensure that motor activity elicited by irrelevant affording objects remains below the threshold for actual movement (Schaefer et al., 2010; McBride et al., 2012, 2013).

In Experiment 1, we tested this "frontal control" hypothesis by "loading" frontal resources with an effortful working memory (WM) task (Mitchell et al., 2002; Kim et al., 2005; Owen et al., 2005). Specifically, we presented affording and nonaffording objects while participants were under high (effortful) or low (noneffortful) WM load. We indexed motor affordances with the well-established electroencephalographic (EEG) signatures of mu ERD and the P300 ERP component over centroparietal electrodes (Pfurtscheller and Neuper, 1997; McFarland et al., 2000; Righi et al., 2014). In accordance with the frontal control hypothesis, we predicted increased affordance effects for the mu ERD and P300 ERP component during high WM load, as fewer resources would be available to control task-irrelevant motor provocations. Following Experiment 1's results, we conducted a second experiment to try to better understand how WM load and the affordance are related.

Materials and Methods

Experiment 1

Participants. Seventeen right-handed, neurologically intact human volunteers (11 females) with normal or corrected-to-normal vision were recruited from the University of California, San Diego (mean ± SD age, 21 ± 3.3 years). Each participant provided written informed consent as required by the local Institutional Review Board at University of California–San Diego. They were compensated $15 per hour. Following preprocessing, data from 3 participants still contained substantial blink, eye movement, and head movement artifacts that resulted in systematic noise across all electrodes, rendering their data unanalyzable. We therefore excluded the 3 participants, which left the data from 14 participants in the final behavioral and EEG analyses. Right-handedness was determined by participants' self-report before arriving and upon arrival.

Behavioral task. Stimuli were presented on a PC running Windows XP using MATLAB (The MathWorks) and the Psychophysics Toolbox (version 3.0.8). Participants were seated 60 cm from the CRT monitor with a white background (60 Hz refresh rate) in a sound-attenuated and electromagnetically shielded room (ETS Lindgren).

The experiment was divided into two stages: the capacity test, followed by the experiment proper. The purpose of the capacity test was to provide an estimate of WM capacity for the high WM load condition in the experiment proper. In the capacity test, each trial began with a fixation cross for a variable intertrial interval period of 2–5 s. Then, a string of black uppercase letters in Arial font appeared at the center of a white screen. The string of letters always consisted of 6, 7, 8, or 9 letters. All letters were chosen randomly from an alphabetic list that excluded only vowels. These letters remained on the screen for 4.5 s. During this time, the word "Memorize" was presented in red color at the top of the screen, as participants were instructed to do their best to read the letters on the screen and hold those letters in WM. After the 4.5 s Memorize phase, there was a 1.875 s interstimulus interval (ISI) before participants were tested on the string of letters. During this period, participants were encouraged to rehearse the letter strings during the retention interval. Next, participants were probed with another letter string to evaluate their performance on the WM task. The probe letter string either identically matched the letters presented in the Memorize phase, or differed such that (only) two adjacent letters switched positions. Thus, the Probe phase always consisted of the same letters as in the Memorize phase, with the only possible change being a switch of two adjacent letters in the string. During the Probe phase, the words "Same or Different?" were displayed at the top of the screen in red. Moreover, the letter string in the probe phase was presented in lowercase Times font to reduce the likelihood that participants could rely on familiarity of the letter string instead of WM. The Probe phase lasted for a maximum of 3.75 s, and participants were instructed to respond both as quickly and as accurately as possible by pressing a keypad button with the right middle finger for "same" and the right index finger for "different." The actual probability of the Probe letter string matching the Memorize letter string was 0.5. There were two blocks of 30 trials in the capacity test phase (60 trials total). The string lengths used (6, 7, 8, and 9) were each presented 15 times. EEG data were not recorded during the capacity test.

Following the capacity test, we plotted the percentage correct (of 15) for each string length and chose the string length that was closest to a 75% correct for the experiment proper (50% correct is chance). This allowed the following: (1) relatively equal high load difficulty and performance across participants; (2) a moderate level of high WM load difficulty that was above chance, yet also taxed WM resources; and (3) a single high WM load string length for each individual, which helped avoid potential confounds of different letter string lengths in the analysis stage.

Next, the experiment proper stage began (Fig. 1). This stage was very similar to the capacity test, but with several key differences. First, on any given trial, the letter string in the Memorize phase consisted of either two letters (low load) or the high WM load string length chosen from the capacity test (i.e., 6, 7, 8, or 9 letters). Regardless of letter string length, participants were given 4.5 s to memorize the string. Second, on 80% of the trials, either an image of a right-handled cup (affording object) or an urn (nonaffording control object) was presented for 750 ms in the center of the screen. The cups used here were used in a previous TMS-EMG experiment that showed an affordance effect via greater MEPs when viewing the cups versus control objects (Buccino et al., 2009). Moreover, the same cups were used in a pilot TMS-EMG experiment we conducted that measured irrelevant affordances in a target detection task and found a significant affordance effect (S.M.F. and A.R.A., unpublished observations). Together, this increased our confidence that viewing the cups potentiated motor activation and thus was sufficiently affording. As for the control objects, urns were chosen to match the physical properties of the cups as best as we could, without the control object having a strong affordance, at least compared with the handled cups. The presentation of the stimulus objects occurred at a variable ISI of 0.75, 1.5, 2.25, or 3 s (occurring with an equal probability) following the Memorize phase. The purpose of the variable ISI times was to make the appearance of the object unpredictable, thus helping ensure that the participant did not avert attention away from the screen. Note that we could not include ISI as part of the statistical analysis because trials numbers would be far too low (<10 trials) for each condition. The images of the cup and urn were randomly selected from a set of five possible images for each object type, and each object had a visual angle of ~6.2° × 6.2°. The total ISI between the Memorize and Probe phases remained constant at 4.5 s. A third difference was that, on 20% of trials (called catch trials), no object image

was presented and the Probe phase occurred in its place. This ensured that participants maintained their attentional focus because they were instructed to respond as quickly and accurately as possible. Finally, the experiment proper had 5 blocks with 40 trials per block (200 total trials). In each block, there were 8 trials per experimental condition (low load affording [low-afford], low load control [low-control], high load affording [high-afford], high load control [high-control]), as well as 4 low load catch trials and 4 high load catch trials per block. Across the entire experiment, this yielded 40 total trials per experimental condition. As in the capacity test phase, the actual probability of the Probe letter string matching the Memorize phase was 0.5.

EEG recording. The continuous EEG data were recorded using a 64 electrode Biosemi ActiveTwo system (Biosemi Instrumentation) at a sampling rate of 512 Hz. The elastic EEG cap covered the head from above the eyebrows to below the inion and the 64 electrodes were equally spaced across the EEG cap. The central electrode Cz was placed right above the vertex located halfway between the nasion and the inion and between the left and right ears. Two additional electrodes were placed at the left and right mastoids, as reference electrodes. Blinks and vertical eye movements were monitored via four extra electrodes placed below and above the eyes. Horizontal eye movements were monitored by another pair of electrodes, placed laterally near the outer canthi of the left and right eyes. The EEG data were referenced on-line to the common mode sense active electrodes/driven right leg passive electrodes and all offsets from the reference were maintained $<20\ \mu V$.

EEG preprocessing. We used EEGlab11.0.3.1b (Delorme and Makeig, 2004) and custom MATLAB scripts to preprocess the EEG data offline. First, we re-referenced the continuous EEG data to the mean of the two mastoid electrodes and applied 0.25-Hz high-pass and 55-Hz low-pass Butterworth filters (3rd order). Then, we rejected prominent eye blink artifacts using independent components analysis from the continuous EEG data (Makeig et al., 1996). Next, the continuous data were segmented into epochs extending from-976 ms before the onset of the object to the end of the trial. Finally, we disregarded epochs contaminated by residual eye blinks, eye movements, excessive muscle activity, or slow-going drifts using threshold rejection and visual inspection (9.62% ± 1.4% of trials were rejected).

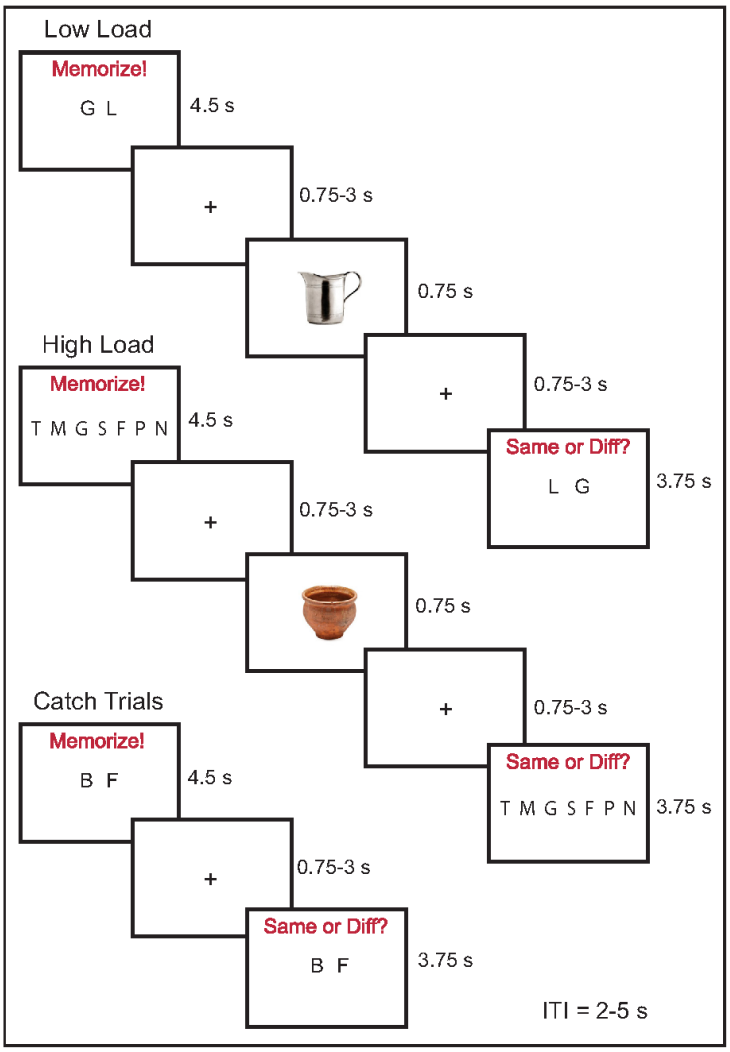

Figure 1. Task design. The Memorize phase consisted of trials with low WM load (2 letters) and high WM load (6–9 letters, determined by a capacity test). Participants held the letter string in WM until the end of the trial. On 80% of trials, either an image of a right-handled cup (affording object) or an urn (nonaffording control object) was presented while the letter strings were held in WM. Finally, during the Probe phase, participants were required to press a button to indicate whether or not the probe letter string identically matched the letter string presented during the Memorize phase. To ensure participants focused on the screen for the entire trial duration, catch trials occurred in which the object image was omitted with the probe occurring in its place.

EEG frequency analysis. To examine differences in mu amplitudes across experimental conditions, we filtered the epoched EEG data using the complex Morlet function in MATLAB (cmor5–3). We then focused on the mu frequency band, which ranges from ~7 to 13 Hz (Arroyo et al., 1993; Pfurtscheller and Lopes da Silva, 1999; Wang et al., 1999). Notably, previous studies have shown that lower (~8–10 Hz) versus upper (~10–12 Hz) frequency bands in the mu range likely correspond to different sensorimotor mechanisms (Pfurtscheller, 2003; Pfurtscheller et al., 2006; Proverbio, 2012; Rüther et al., 2014). We therefore analyzed lower and upper mu rhythms separately, with a frequency range of 7–10 Hz and 10–13 Hz for low and high mu rhythms, respectively (we used a slightly broader range than previous studies to capture all possible mu-related activity). Based upon a recent study that analyzed affordances based on lower and upper mu frequency bands (Ruther et al., 2014), we expected the affordance to take place in the lower mu frequency range.

We investigated mu ERD in three selected centroparietal electrodes (Cz, CPz, Pz), which was based on the topographic maps of past studies that found mu ERD motor affordance effects (Proverbio, 2012; Kumar et al., 2013). These studies tended to show affordance-related ERD at more midline and posterior sensorimotor areas than classic ERD studies examining actual and planned movements (Pfurtscheller and Aranibar, 1979; McFarland et al., 2000). To test for mu amplitude differences, we focused on a relatively broad time window of 100–750 ms after the onset of the object. We tested for mu amplitude differences in lower and upper mu frequency bands separately using two-way repeated-measures

ANOVAs with factors of Load (high/low) and Object (affording/control). The ANOVAs were followed by planned contrasts to examine potential differences in the affording versus control object for both high and low load.

In addition, past studies have shown that frontal theta activity (~4–7 Hz) is an index of the involvement of frontal cortex in WM processes, including the maintenance and manipulation of WM contents (Gevins et al., 1997; Jensen and Tesche, 2002; Onton et al., 2005; Pesonen et al., 2007; Mizuhara and Yamaguchi, 2011; Itthipuripat et al., 2013; Hsieh and Ranganath, 2014). In general, it has been shown that frontal theta activity increases with WM load (Gevins et al., 1997; Jensen and Tesche, 2002; Onton et al., 2005; Pesonen et al., 2007). Thus, to confirm that our task manipulation successfully manipulated WM load, we analyzed frontal theta activity in the low and high load conditions over midline electrodes (AFz, Fz, and FCz). We filtered the data from 4 to 7 Hz (with the same procedure as mu ERD), and compared differences in theta amplitude across high and low load conditions from −750–0 ms before the onset of the object (without baseline correction). We then used a paired *t* test to analyze potential differences between high and low load.

ERP analysis. In addition to the EEG frequency analysis, we compared amplitude differences of ERPs across all experimental conditions. To do so, we first subtracted the −100–0 ms pre-object baseline from the artifact-free epoched data and computed the average of the object stimulus-locked EEG data for each participant using a standard averaging procedure (Luck, 2005). Then, we averaged the data across all participants to obtain the grand-average ERPs for low-afford, low-control, high-afford, and high-control conditions. In this analysis, we focused on the following: (1) the early positive potential P1 (peaking at 90 to 120 ms in left and right posterior-occiptal electrodes; i.e., O1, PO3, PO7 for left and O2, PO4, PO8 for right) to confirm that there were no general perceptual difference in object processing across WM load conditions; and (2) the later positive potential P300 (peaking at 300 to 500 ms at the centroparietal electrodes; i.e., Cz, CPz, Pz) because past studies have found higher P300 amplitude for affording versus nonaffording stimuli (Proverbio et al., 2011; Righi et al., 2014). For the P100 analysis, we used a three-way repeated-measures ANOVA to compare mean amplitude differences for the factors of Load (high/low), Object (affording/control), and Hemisphere (right/left) because early visual processing of the right-handled cup was likely to show hemispheric differences. For the P300 analysis, we used a two-way repeated-measures ANOVA to compare mean amplitude difference for the factors of Load (high/low) and Object (affording/control) in the midline centroparietal electrodes.

Experiment 2

We used long-interval paired-pulse transcranial magnetic stimulation (ppTMS) over primary motor cortex (Nakamura et al., 1997; Chen et al., 1999; McDonnell et al., 2006). This method lets one measure long-interval cortical inhibition (LICI). LICI has been shown to relate to gamma-aminobutyric acid-B ($GABA_B$) tone in primary motor cortex (McDonnell et al., 2006; Kohl and Paulsen, 2010). To measure LICI, one compares the amplitude of the MEP from a single test pulse with the amplitude of a test pulse that is preceded by a conditioning pulse, typically 50–200 ms earlier. The conditioning pulse putatively activates $GABA_B$ interneurons, and this attenuates the amplitude of the test pulse, compared with the nonconditioned test pulse.

Participants. Twenty right-handed, neurologically intact human volunteers (8 females) with normal or corrected-to-normal vision were recruited from the University of California, San Diego (mean ± SD age, 20.5 ± 1.7 years). Each participant provided written informed consent as required by the local Institutional Review Board at University of California–San Diego. They were compensated $15 per hour. Four subjects were excused before participating in the experiment proper because there was excessive EMG noise (specifically, EMG values consistently exceeded our cutoff criterion of 0.01 mV) during threshholding and in the intertrial baseline during the capacity test. It was later determined that this related to an equipment malfunction that was subsequently fixed. This left data from 16 participants in the final behavioral and TMS analyses.

Behavioral task. The behavioral task was almost identical to the design in Experiment 1, with a few small exceptions to adjust for the ppTMS method used in Experiment 2. First, instead of 5 total blocks in the experiment proper, there were now 6 blocks to allow for more TMS pulses. Second, the total ISI between the Memorize and Probe phases remained constant at 4.0 s (instead of 4.5 s) to allow for more trials. Third, instead of making a button press with the right hand, participants were instructed to respond verbally into a microphone by saying "true" if they thought that the trial was a match and to not respond at all if they thought that it was not a match. This helped avoid any possible contamination of the electromyography (EMG) signal due to preparatory hand movement and minimized the amount of action required on a given trial. To determine whether a response was made, audio files from each trial were analyzed via visual inspection for both amplitude and shape of the response.

Paired-pulse TMS procedure details. TMS pulses were generated with a MagStim 20–2 monophasic stimulator connected to a MagStim BiStim module (Magstim) and a 70 mm figure-of-eight coil. Surface EMG was recorded from the first dorsal interosseous muscle of the right hand via 10 mm-diameter Ag-AgCl hydrogel electrodes (Medical Supplies).

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. The maximum MEP size was determined by increasing TMS stimulus intensity in 3%–4% increments until the MEP amplitude no longer increased. Then, the TMS stimulus intensity was adjusted to produce MEPs that were approximately half of the maximum MEP amplitude while the participant was at rest. Once a half-maximum TMS stimulus intensity was established, ppTMS was applied while the participant was at rest, such that TMS pulses alternated between paired and single pulses (note that TMS stimulus intensity is the same for both pulses). All paired pulses throughout the experiment were delivered at a 100 ms ISI, which is an effective ISI to evoke LICI that reflects supraspinal inhibition in the motor cortex (Nakamura et al., 1997; Chen et al., 1999; McDonnell et al., 2006; Chu et al., 2008). The TMS stimulus intensity was adjusted until it was verified that (1) the nonconditioned pulse (NP) continued to elicit half-maximum MEP amplitudes and (2) the test pulse (TP) elicited a ~50% inhibition. This procedure was then repeated during the capacity test to confirm that the TMS stimulus intensity continued to meet the above criteria in a task setting. The mean TMS stimulus intensity across participants was 51.9 ± 9.6% stimulator output. An examination of the root mean square values for the 100 ms time window before the TMS pulse showed no significant main effects or interactions (all *p* values >0.34), demonstrating that the MEP patterns described below were not contaminated by differences in the pre-TMS period.

During the experiment proper, single and paired-pulse trials were presented randomly to avoid predictions regarding pulse type. The pulse was delivered either before or after the onset of the object. To reduce predictability of the pulse timing, the pulse was presented either 300 or 500 ms before or after the object onset. All trials types were fully counterbalanced within each experimental block.

LICI analysis. An EMG sweep started 200 ms before stimulation. MEPs were identified from the EMG using in-house software developed in MATLAB (The MathWorks). To ensure participants were at rest before the MEP, trials were excluded if the root mean square EMG in the 100 ms before the TMS pulse was >0.01 mV. To ensure an MEP was generated on a given trial, trials were excluded if the MEP of the NP was <0.05 mV (during single-pulse trials) or if the MEP of both the conditioning pulse and the TP were <0.05 mV (during paired-pulse trials). Finally, we also excluded trials if the amplitude maxed out at 1 mV or −1 mV because we used a CED MICRO 1401 system that has a cutoff at 2 mV (range 1 to −1) and thus we could not be sure of the true MEP amplitude when it exceeded 2 mV (e.g., 2.1 mV, 4 mV, etc.). For this reason, we elected to exclude such MEPs that "maxed out," as we feel that this provides the most accurate version of the MEP dataset. The mean percentage of excluded trials across participants was 5.89 ± 0.92%, and there was no significant difference in the number of excluded trials for low and high WM load ($t < 1$). Mean peak-to-peak amplitudes of MEPs were calcu-

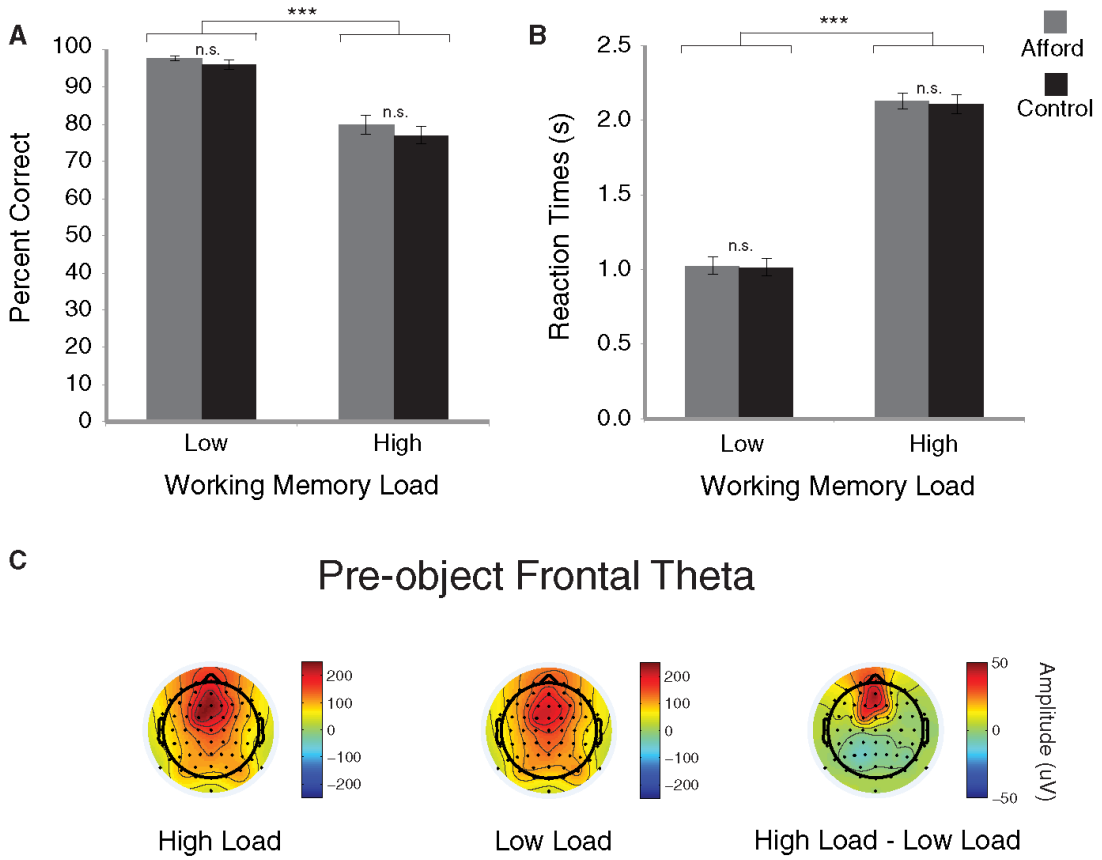

Figure 2. Behavior and pre-object frontal theta. ***A***, Percent correct was significantly higher on low versus high load trials. ***B***, RTs were significantly shorter on low versus high load trials. ***C***, Frontal theta amplitude measured before the onset of the object was significantly greater for high versus low load ($p < 0.05$). Together, these results demonstrate that the WM manipulation was effective. Error bars indicate SEM. ***$p < 0.001$. n.s., Not significant.

lated for all conditions. The pulse times of 300 and 500 ms preceding or following the object were collapsed, as the two pulse times only served to reduce predictability among participants. LICI was calculated for each participant and in each condition using the following formula: LICI(%) = [1 − (TP/NP)] × 100, where TP is the median test pulse MEP amplitude and NP is the median nonconditioned pulse MEP amplitude. Thus, 100% inhibition reflects complete abolition of the TP MEP amplitude whereas 0% inhibition reflects no effect of the conditioning stimulus (Coxon et al., 2006). LICI values were then entered into a repeated-measures ANOVA with factors of Load (high/low) and Time (before/after). Although affording and control stimuli were used to match Experiment 1's design, the object type was not a factor in the analysis, as the goal was to measure LICI rather than the affordance.

Results

Experiment 1

Behavior

For high load, the average WM letter string length was 8.07 (SD = 0.73), and the percentage correct was 80 ± 2%, closely matching the target percentage correct of 75%. Our load manipulation was effective, as percentage correct for high load was significantly lower than for low load (96 ± 41%, $t_{(13)} = 10.5$, $p < 0.001$; Fig. 2*A*). Similarly, mean RTs in high load (2.13 ± 0.06 s) were significantly slower than in low load (1.04 ± 0.06 s, $t_{(13)} = 16.8$, $p < 0.001$; Fig. 2*B*).

Midline frontal theta

As another validation of WM load, we examined frontal theta amplitude. This was significantly increased in the 750 ms period before the object (affording or control) for the high compared with low load WM conditions ($t_{(13)} = 2.81$, $p = 0.01$; Fig. 2*C*). This is consistent with previous studies (Gevins et al., 1997; Jensen and Tesche, 2002; Sauseng et al., 2010; Itthipuripat et al., 2013).

Mu ERD

Mu ERD is a standard measure of motor affordance and greater mu ERD has been directly linked to larger MEPs in M1 (Takemi et al., 2013). As a previous mu ERD affordance study only observed the affordance effect in the lower portion of the mu frequency range (Ruther et al., 2014), we analyzed lower (7–10 Hz) and higher (10–13 Hz) mu frequency bands separately Load (high/low) and Object (affording/control) as factors.

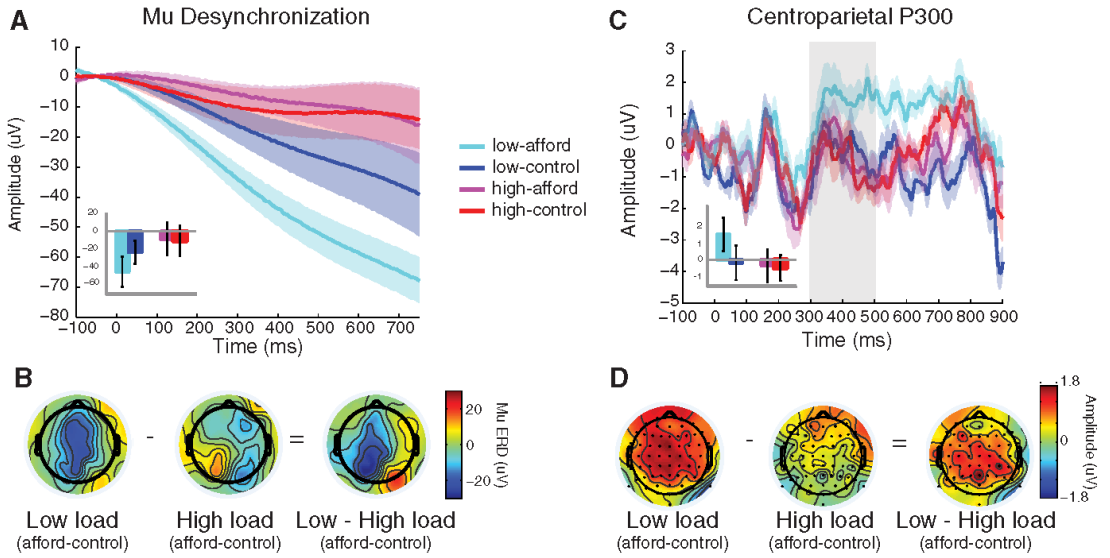

Figure 3. Electrophysiological affordance measures for centroparietal midline electrodes. ***A***, For the low load condition, there was significantly greater mu desynchronization (in the 7–10 Hz range) for the affording versus the control object, demonstrating an affordance effect. There was no difference in mu desynchronization in the high load condition. ***B***, The topographic map for the mu desynchronization showed a strong affordance effect over centroparietal electrodes (Cz, CPz, Pz) in the low load condition, whereas the topographic map for the high load condition showed no evidence of an affordance effect anywhere in the brain. The interaction between Load and Object was strongest for more posterior regions of the left hemisphere. ***C***, For the low load condition, the amplitude of the P300 ERP was significantly greater for the affording object compared with the nonaffording control object. This was consistent with the mu desynchronization results, as was the lack of a difference in P300 amplitude in the high load condition, resulting in a significant interaction. ***D***, The topographic map for the P300 shows a strong affordance effect over centroparietal electrodes in the low load condition, yet no differences in the high load condition.

For the lower mu frequency range (7–10 Hz), ANOVA showed a significant main effect of Load ($F_{(1,13)} = 5.15$, $p = 0.04$), with the low load showing overall greater mu ERD than the high load condition. Moreover, there was a nearly significant Load × Object interaction ($F_{(1,13)} = 4.5$, $p = 0.054$), whereby mu ERD was diminished under the high WM load (Fig. 3*A*,*B*). Planned *t* tests showed a significant mu ERD for the affording versus control object in the low load condition ($t_{(13)} = 2.71$, $p = 0.02$), but not in the high load condition ($t < 1$). Moreover, mu ERD for the affording object was significantly greater for low load compared with high load ($t_{(13)} = 3.7$, $p = 0.003$), whereas the control object showed no load differences ($t < 1$). We also tested mu ERD in left hemisphere centroparietal electrodes immediately adjacent to the midline (C1, CP1, and P1) because all the cups were right handled, and found a significant main effect of Load ($F_{(1,13)} = 5.82$, $p = 0.03$), as well as a significant Load × Object interaction ($F_{(1,13)} = 5.57$, $p = 0.03$).

For the upper mu frequency range (10–13 Hz), ANOVA showed no significant main effects or interactions in mu ERD (*F* values <1). These results are consistent with a previous study that found mu ERD affordance effects in the lower, but not the upper, frequency range (Rüther et al., 2014).

Centroparietal P300

The centroparietal P300 is another measure of the motor affordance. ANOVA revealed a significant Load × Object interaction ($F_{(1,13)} = 6.18$, $p = 0.03$), with higher centroparietal P300 amplitude for the affording versus the control object in the low load condition ($t_{(13)} = 3.36$, $p = 0.005$), yet no affordance effect in the high load condition ($t < 1$) (Fig. 3*C*,*D*). This is consistent with the lower frequency mu ERD results.

Posterior-occipital P100

To test whether WM load may have differential effects on early perceptual processing for the affording and control object stimuli, we examined the amplitude modulation of the posterior-occipital P100. The P100 is a suitable ERP component to address this question because the modulation of the P100 has been linked to early sensory gain in visual cortex and early perceptual processing of visual stimuli (Van Voorhis and Hillyard, 1977; Woldorff et al., 1997; Hillyard and Anllo-Vento, 1998; Itthipuripat et al., 2014). ANOVA with factors of Load (high/low), Object (affording/control), and Hemisphere (left/right) revealed a significant main effect of Object ($F_{(1,13)} = 5.88$, $p = 0.03$), with the affording object showing a higher amplitude than the control object. There was also a significant Object × Hemisphere interaction ($F_{(1,13)} = 10.16$, $p = 0.007$). Follow-up ANOVAs that analyzed the two hemispheres separately with Object and Load as factors showed a significant main effect of Object in the left hemisphere ($F_{(1,13)} = 12.15$, $p = 0.004$), but not in the right hemisphere ($F < 1$) (Fig. 4) (for a similar result, see Goslin et al., 2012). Notably, left hemisphere electrodes showed significant affording versus control object differences in both low load ($t_{(13)} = 2.92$, $p = 0.01$) and high load ($t_{(13)} = 2.28$, $p = 0.04$) conditions. The greater P100 amplitude to the affording object (right-handled cups) occurred because the handle was likely the most salient feature of the cup and therefore showed greater visual processing in the contralateral left hemisphere, resulting in a larger P100 response. These results are consistent with a prior affordance study (Goslin et al., 2012). Such lateralized early visual processing did not occur when the urn appeared, as no features of the urn were more salient than others. Importantly, neither hemisphere showed a significant

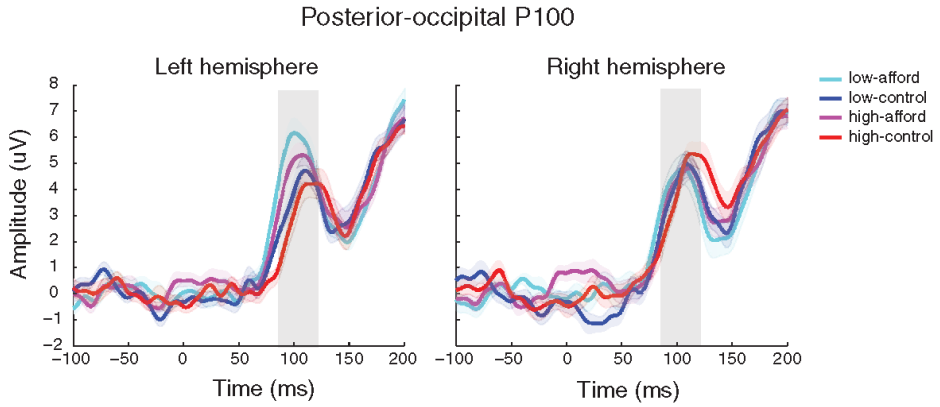

Figure 4. Posterior-occipital P100. While the right hemisphere (right panel) showed no significant effects, the P100 amplitude in the left hemisphere (left panel) was significantly greater for the affording versus the control object during both low load and high load. Notably, there was no difference in P100 amplitude between low and high load, nor was there an interaction between Load and Object. This demonstrates early visual processing for the affording object was selective to the contralateral hemisphere (i.e., the right handled cup in the left hemisphere) and that early sensory perception was not significantly different between high and low WM load.

Load × Object interaction or a main effect of Load (all p values >0.18), suggesting that the mu ERD and P300 results were not driven by differences in early perceptual processing across WM loads.

Theta correlations with mu ERD

Above we reported greater theta activity over frontal electrodes for high versus low load before the onset of the object. Notably, lower frequency mu ERD in left hemisphere centroparietal electrodes showed a significant Load × Object interaction, in which only the low load condition showed an affordance effect (i.e., greater mu ERD for affording vs control object). This suggests that greater engagement of frontal regions (frontal theta prior to the object presentation [−750 to 0]) could relate to the diminished affordance effect (mu ERD after the onset of the affording versus control object) during high load. To test this, each participant's pre-object theta amplitude in the low load was subtracted from the their pre-object theta amplitude in the high load to obtain a participant-specific theta "load effect" value (i.e., a higher number indicates more frontal theta activity in high load compared to low load). To calculate a mu ERD interaction value for each participant, left hemisphere centroparietal mu ERD for the control object was first subtracted from the affording object, yielding a separate affordance value for low and high load. Then, the low load affordance value was subtracted from the high load affordance value to obtain a participant-specific mu ERD "interaction effect" value. Because greater mu ERD is indicated by more negative values, a larger interaction value means that there is a greater affordance effect for low load compared with high load (e.g., if the low load affordance effect = −50 [large affordance] and the high load affordance effect = −5 [small affordance], then the interaction value would be calculated as (−5) − (−50) = 45, yielding a large positive interaction value). All values were then z-scored, and we correlated the mu ERD interaction effect values against the theta load effect values. There was a significant correlation ($r_{(13)} = 0.56$, $p = 0.037$), such that participants with greater high load pre-object theta activity (relative to low load) showed a more diminished affordance effect in the high load compared with the low load (Fig. 5). This provides further evidence that greater WM load is associated with a reduced affordance.

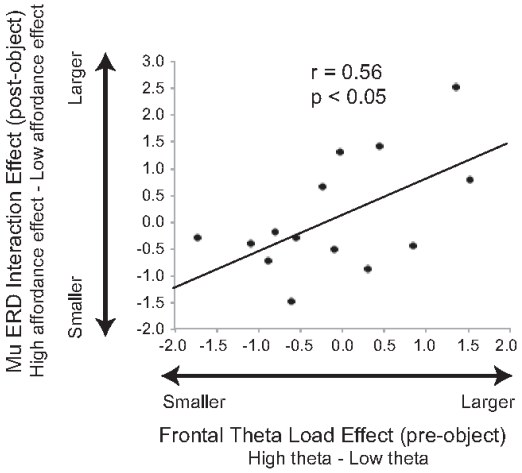

Figure 5. Relationship between frontal theta and mu ERD across participants. The frontal theta load effect represents the engagement of frontal regions during high versus low load. A frontal theta load effect value was calculated for each participant by subtracting the low load pre-object frontal theta amplitude from the high load amplitude. The mu ERD interaction effect represents the degree to which a mu ERD affordance occurred during low load compared with high load in left hemisphere centroparietal electrodes (C1, CP1, P1). A mu ERD interaction effect value was calculated by subtracting the low load mu ERD affordance effect (affording vs control object) from the high load mu ERD affordance effect, yielding an interaction value (see text for further explanation). There was a significant correlation, such that participants with greater high load pre-object theta activity (relative to low load) showed a larger affordance effect for low compared to high load, indicated by a larger interaction value.

Experiment 2

Experiment 1 showed that increasing WM load reduced the affordance effect. Yet, the mechanism underlying the reduced affordance is still unclear. One possibility is that being in a state of high WM is concomitant with greater sustained inhibitory activity in the motor system (i.e., the motor system is "set" into a suppressed state for the entire duration of the high load trial) (compare Sauseng et al., 2013). As a result, task-irrelevant motor

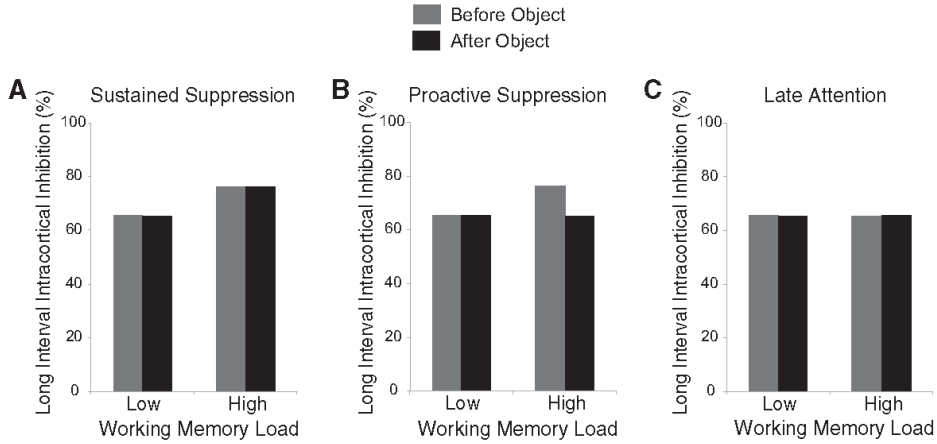

Figure 6. Predictions for different accounts underlying the diminished affordance during high WM load from Experiment 1. ***A***, For the sustained suppression account, suppression in M1 occurs when WM resources are engaged. It predicts greater LICI over M1 for high versus low load both before and after the presentations of the object. ***B***, For the proactive suppression account, there is greater motor suppression during high load to reduce the potentially distracting influence of the task-irrelevant object. It predicts greater LICI over M1 for high versus low load only before the object is presented because it is no longer necessary following the object. ***C***, For the late attention account, the diminished affordance during high load is due to reduced attention during the later stages of object processing. It predicts no differences in LICI over M1 for high versus low load.

affordances can no longer potentiate the motor system in the normal fashion, resulting in a diminished affordance effect.

A variant of this account is that, rather than being in a sustained state of suppression, the participant proactively engaged a suppression mechanism just before the anticipated object occurred in an effort to reduce irrelevant, potentially distracting, motor provocations. This would perhaps be particularly important under high load because, according to Lavie's load theory, the potential for distraction is greatest during high WM load due to a reduced capacity to filter the distractors (Lavie et al., 2004).

An entirely different account is that the affordance was reduced under high load because the participant did not attend properly to the object. There are, however, several immediate challenges to this account. First, the P100 results showed higher amplitude for the affording versus control object in the left hemisphere (the contralateral hemisphere to the rightward-facing cup handle) under both low and high load, with no main effect of Load or interaction between Object and Load. As modulation of the P100 has been linked to early perceptual processing of visual stimuli (Van Voorhis and Hillyard, 1977; Woldorff et al., 1997; Hillyard and Anllo-Vento, 1998; Itthipuripat et al., 2014), this result suggests that early attentional processing was not different across loads. Second, several studies found that attentional orienting toward the affording object does not influence the affordance effect (Tucker and Ellis, 2004; Symes et al., 2007; Riggio et al., 2008). In one study (Riggio et al., 2008), the authors used offset stimuli to manipulate the automatic allocation of attention before response selection and execution. Their results showed an affordance effect even when the affording object was not visible during response selection and, more generally, that it occurred independently of the amount of attentional orienting. This has led researchers to characterize affordances as motor potentiations that emerge quickly (i.e., within 150 ms) and somewhat automatically (Tucker and Ellis, 2004; Symes et al., 2007; Sumner and Husain, 2008; Franca et al., 2012; Goslin et al., 2012). Notwithstanding these points, we could not rule out the possibility that later attentional processing of the objects (e.g., >150 ms after object onset) was reduced during high load, resulting in a diminished affordance effect.

We now aimed to disambiguate the above-mentioned possible accounts of the diminished affordance. Because the ISI period before the cup was variable and relatively long (0.75–3 s), both of the "suppression" accounts above predict that the suppression would be sustained over a time period of several seconds. We therefore measured LICI over M1 because LICI is generally associated with a more tonic form of inhibition, thought to reflect the slower $GABA_B$ receptor signaling (Kohl and Paulsen, 2010). On the sustained suppression account, the motor system (perhaps primary motor cortex) is "set" into a suppressed state throughout the high WM load trial (before and after the object); on the proactive suppression account, the motor system is "set" into a suppressed state only before the object; and on the attention account, the motor system has nothing to do with the reduced affordance.

TMS pulses were delivered both before and after the object presentation to examine whether any differences in LICI would be present only before the object onset or sustained throughout the WM retention interval. Given this design, each account makes distinct predictions (Fig. 6). If the diminished affordance observed in Experiment 1 is due to increased sustained suppressive activity while in a state of high WM, then this predicts greater LICI for high versus low load through the WM retention interval (i.e., a main effect of Load; Fig. 6*A*); if it is due to increased suppressive activity that proactively prevents the task-irrelevant affordance to reduce potential distraction, then this predicts greater LICI for high versus low load before, but not after, the object (i.e., an interaction between Load and Time; Fig. 6*B*); if the diminished affordance is due to reduced late attentional processing of the objects during high load, then this predicts no difference in LICI at M1 (i.e., no main effects or interactions; Fig. 6*C*).

Behavior

The behavioral results for Experiment 2 largely resembled those from Experiment 1. For high load, the average WM letter string length was 8.44 (SD = 0.73) and the percentage correct was 78 ±

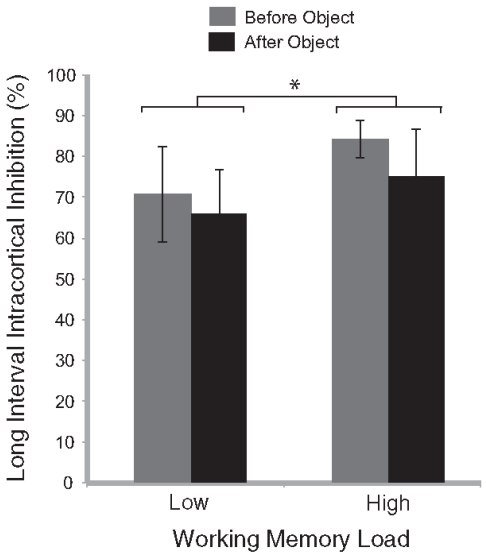

Figure 7. Experiment 2 results. LICI over M1 was greater for high versus low load. This supports the sustained suppression account for the diminished affordance effect during high load, in which greater WM engagement leads to a concomitant increase in inhibitory activity over motor regions. LICI was calculated using the following: LICI (%) = [1 − (TP/NP)] × 100, where TP is the test pulse and NP is the nonconditioned pulse. Error bars indicate SEM. *$p < 0.05$.

Table 1. Mean MEP amplitudes across participants for each condition[a]

	Pre		Post	
	NP	TP	NP	TP
Low load	0.418 (0.14)	0.103 (0.13)	0.408 (0.17)	0.104 (0.11)
High load	0.618 (0.23)	0.092 (0.11)	0.540 (0.16)	0.096 (0.13)

[a]Data are given as mV: mean (SD).

2%), closely matching the target percentage correct of 75%. The load manipulation was successful, as percentage correct for high load was significantly lower than in low load 98 ± 0.25%; $t_{(15)} = 11.6$, $p < 0.001$), and mean RTs in high load (2.39 ± 0.06 s) were significantly slower than in low load (1.04 ± 0.04 s; $t_{(15)} = 22.7$, $p < 0.001$). There were no significant differences for percentage correct or RTs when comparing affording versus control trials (all p values >0.26).

LICI

For the TMS analysis, ANOVA with the factors of Load (high/low) and Time (before/after the object) and the dependent measure of LICI showed a significant main effect of Load. Specifically, there was greater LICI for high (79.6% inhibition) compared with low (68.3% inhibition) WM load ($F_{(15)} = 5.34$, $p = 0.036$; Fig. 7). There was also a marginally significant main effect of Time ($F_{(15)} = 4.22$, $p = 0.058$), such that LICI was generally greater before object onset (77.5% inhibition) compared with after (70.4% inhibition). Notably, there was not a significant Load × Time interaction ($F < 1$). As can be seen from Figure 6, these results support the sustained suppression account. The mean NP and TP data for both time periods are presented in Table 1. An increase in the NP amplitude during high load is contributing to the difference in LICI, which is not surprising because high load likely elicits greater physiological responses that can influence the MEP (e.g., stress and arousal). Despite the NP amplitude increase under high load, the TP in the high load condition remained low, indicating an inhibitory influence in M1 during high load.

Discussion

We tested whether WM load influences motor potentiation from affording objects. We predicted that high load would increase the motor affordance, which was measured via mu ERD and the P300 ERP component over centroparietal electrodes. Under low load, there was a motor affordance: low-frequency mu ERD was greater for affording versus nonaffording control objects, consistent with previous research (Rüther et al., 2014). Contrary to our prediction, Experiment 1 showed that, for both EEG neural measures (mu ERD and P300 amplitude), the affordance effect was present during low, but not high, WM load. A subsequent exploratory analysis indicated that individuals with greater WM-related neural activity (measured via pre-object frontal theta activity) showed a larger interaction effect (measured via mu ERD activity) in high versus low load. Note that a larger interaction value indicates a larger affordance effect for low compared to high load. This shows that the increase in frontal theta activity during high WM load is related to reductions in task-irrelevant motor provocations. We explored the mechanism responsible for the diminished affordance in Experiment 2 using ppTMS to measure long-interval cortical inhibition (LICI) over M1 during high load versus low load. Results showed greater LICI in M1 during high compared low load, and that this was not dependent on the timing of the LICI measurement (before versus after the object). This suggests that the reduced affordance under high load in Experiment 1 was due to increased sustained suppression of M1. These findings provide new insights into the interaction between WM and the inhibitory state of M1 and also speak to the extent to which affordances are or are not automatic.

Implications

The results across the two studies show that high WM load reduces the motor affordance and increases intracortical inhibition in M1. Putting these together, we suppose that high load "sets" the motor system into a suppressed state; and, because of this, the incipient affordance cannot get expressed in the same way. We suppose that greater intracortical inhibition during high load prevents mu desynchronization, which is thought to reflect a reduction of intracortical inhibition and increased pyramidal neuron firing in M1 (Leocani et al., 2001; Takemi et al., 2013; for a different paradigm, compare Hummel et al., 2002).

Although it is intuitively true that being in a concentrated state prevents processing of incoming sensory information, there are exceptions to this (e.g., Lavie's demonstrations that there is more distractibility under high WM load; Lavie et al., 2004). Regardless, here we specifically show that being under high WM load has effects on M1, and we suppose these effects mitigate a motor affordance (which, to our knowledge, is a novel finding). This speaks to a second implication of our study, which is the automaticity of motor affordances. Many studies have argued that affordances are automatic, as they can occur even in the absence of focused attention on the object (Leocani et al., 2001; Riggio et al., 2008; McBride et al., 2012; Takemi et al., 2013). However, the current results indicate that whether an affordance is expressed may also rely on an indi-

viduals' current cognitive state (i.e., high vs low WM load). This suggests that subthreshold motor provocations do not necessarily occur all the time. Rather, the strength and potential influence of such provocations depend on the excitatory/inhibitory state of the motor system at the time when the object is viewed (Knight et al., 1999). Notably, while in the current study we observed this interaction using motor affordances, it is possible that the same principles apply for other types of motor provocations, including learned stimulus–response pairings (e.g., in the Flanker or Stroop tasks) and motivationally triggered provocations (Freeman et al., 2014; Freeman et al., 2015).

A third implication of our results concerns individuals with attention deficit hyperactivity disorder (ADHD), who have substantial WM problems (Rapport et al., 2008; Raiker et al., 2012), reduced intracortical inhibition (Gilbert et al., 2004, 2011; Buchmann et al., 2007), increased motor hyperactivity (at least for some forms of ADHD) and poor specific (Lijffijt et al., 2005) and general (Barkley, 1997) response inhibitory control abilities. In light of the current study, which links increased WM load to increased intracorical inhibition at M1, one might wonder whether there is a similar relation in the case of ADHD. It is possible that deficient WM and reduced intracortical inhibition at M1 in ADHD are related and that this results in increased motor provocation and distractibility from task-irrelevant objects.

Limitations and future questions

This study has some limitations. First, we deliberately used a task that did not require button presses/responses for the affording/control object (instead, we operationalized the affordance physiologically alone). Although this obviated any dual task effects, it meant that we had no behavioral index of the affordance, thus limiting our ability to link neural and behavioral measures. Second, in Experiment 2, there was no physiological index of affordance; thus, we have to infer that an affordance did occur. Future studies could use combined EEG and ppTMS to try to directly relate changes in intracortical inhibition with changes in the affordance in the same experiment. Alternatively, single-pulse TMS could be used at specific time points after the affordance, in the same experiment as ppTMS to index LICI. Third, we only measured motor excitability from the right index finger muscle, which was behaviorally relevant to the affording object (right-handled cup). It is therefore unclear whether we would have observed increased LICI across all muscles in the motor system, or whether the effect was more restricted to behaviorally relevant muscles. Fourth, although we sampled pulse times before and after the object, we cannot know whether increased LICI was truly sustained across the entire WM delay period or whether it was a more phasic process that occurred near the time of object presentation. Finally, because we did not collect control LICI data in a resting state, we cannot rule out the possibility that there was less inhibition in the low WM condition compared with rest and high load. However, we believe this is unlikely for two reasons. First, the targeted inhibition during the thresholding procedure (when the participant was at rest) was 50%, which is far below the 70% inhibition we observed during low WM load. Second, while our LICI results (increased inhibition for high WM, which likely corresponded to a mitigation of the affordance in Experiment 1) are consistent with a sustained-suppression-under-high-WM account, we cannot think of any theory compatible with the pattern of results where there is less inhibition under low load compared with rest and high load.

In conclusion, whereas we predicted that being under higher WM load would deplete frontal resources and enhance the affordance effect, we found that the affordance effect was instead diminished under high load. In Experiment 2, we found increased long-interval cortical inhibition over M1 during high load, suggesting that a sustained suppression of motor activity over M1 prevented the affordance from being generated. These results suggest a close connection between WM-related neural activity and the balance of excitatory and inhibitory activity in the motor cortex. They also provide insights into when and how task-irrelevant motor provocations can be prevented from influencing the motor system. Importantly, these insights may help provide a link between well-known behavioral and brain-related dysfunctions in ADHD.

Notes

Raw data for this article are available at https://github.com/scott-freeman/Freeman-Itthipuripat-and-Aron. This repository contains behavioral and EEG data for Experiment 1 and behavioral and TMS data for Experiment 2. Supplemental material for this article is available at the same URL. This includes Excel files with raw data and also unpublished observations that have not been peer-reviewed.

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Chapter 5, in full, is a reprint of the material as it appears in *Journal of Neuroscience*. Freeman, Scott M.; Itthipuripat, Sirawaj; Aron, Adam, R., 2016. The dissertation author was the primary investigator and author of this paper.

GENERAL DISCUSSION

This dissertation investigated the role of response suppression in controlling motivationally driven action tendencies. Under this overarching goal, six specific aims were addressed: 1) to develop a new paradigm that requires participants to control a motivationally-driven action tendency, 2) examine if, when, and how response suppression is part of such control, 3) investigate if response suppression has any downstream effects on provocation (e.g., can reduce the future impact of provocations), 4) explore response activation and suppression in a sample of overweight individuals, 5) elucidate the motor dynamics of both the activation and suppression processes, and 6) extend the investigation of response suppression to another type of real-world provocation. Below I review the results from Chapters 1-5 and discuss how the results fit into the wider framework of self-control.

In Chapter 1, we developed a novel paradigm to test the hypothesis that controlling a motivationally driven action tendency can be accomplished via response suppression. The paradigm combined an equiprobable go-nogo task with Pavlovian-to-instrumental transfer (PIT)—a phenomenon where the motivation for a reward-driven action (e.g., press to get juice) increases in the presence of a Pavlovian stimulus (e.g., a color associated with a juice reward) (Corbit, Janak, & Balleine, 2007; Prévost, Liljeholm, Tyszka, & O'Doherty, 2012; Talmi, Seymour, Dayan, & Dolan, 2008). Following classic PIT tasks, the go-nogo/PIT task had three phases: 1) in the Instrumental phase, thirsty participants learned to press a button to get juice on go trials and to withhold responding on nogo trials; 2) in the Pavlovian phase, they learned which color (green or purple)

predicted juice delivery (i.e., CS+ or CS-); and 3) in the Transfer phase, on go trials, they again pressed to get juice, but now with a motivating (CS+) or non-motivating (CS-) stimulus in the background; while, on nogo trials, responding was withheld in the presence of the CS+ or CS- stimulus. For all analyses using this task, the primary focus was comparing CS+ to CS- trials in the Transfer phase.

Our behavioral results showed that participants were highly provoked by the CS+ (compared to the CS-) stimulus. This was evident in invigorated instrumental responding and greater motor excitability on go trials, as well as more commission errors on nogo trials. The latter result indicates that the go-nogo/PIT task is well suited to probe the core question of this study: is response control recruited to mitigate a motivationally driven provocation? To answer this question, we analyzed motor excitability on correct nogo trials 250 ms after stimulus onset. We found that motor excitability was reduced beneath baseline for the CS+ (but not the CS-). This beneath-baseline activity provides strong evidence that response suppression can be used to mitigate an action tendency that is motivationally driven. Based on these data, we hypothesized an activation-suppression dynamic on correct nogoCS+ trials, where the CS+ stimulus generates an early activation (probably around 100-150 ms), followed by suppression over that activation (by around 250 ms). We also hypothesized minimal response activation on nogoCS- trials, thus requiring no real suppression. In Chapter 4, we tested this hypothesized model more directly. But first, we wanted to know if suppressing a motivationally driven action tendency has any downstream effects on future provocation.

The goal of Chapter 2 was to investigate the possibility that suppressing a motivational provocation more often can actually reduce the future impact of that

provocation. We tested this idea by varying the proportions of nogoCS+ and nogoCS- trials in three independent groups of participants, while holding the proportions of goCS+ and goCS- trials constant. We then evaluated if increasing the number of nogoCS+ trials affected the quick response activation generated on goCS+ trials, which was measured using first press reaction times (RTs). We found that as the proportion of nogoCS+ trials increased, the PIT effect (goCS+ RT minus goCS- RT) decreased. While we considered several potential accounts that could explain this effect, the results were best explained by what we referred to as a "proactive control" account. Specifically, following nogoCS+ trials, our data indicate that a control mechanism was transiently in place to prevent the CS+ from provoking the motor system on the next trial. If a CS- occurred on the next trial, it was unaffected by the previous trial type. Thus, while Chapter 1 provides evidence for reactive suppression following a motivational provocation, Chapter 2 demonstrates that a proactive suppression mechanism can prevent motivational provocations from taking place.

Chapter 3 expands on the results from Chapters 1 and 2 by testing the go-nogo/PIT paradigm on individuals who varied greatly on weight and reward eating drive (RED). Counterintuitively, our results show that individuals with high (versus low) RED are *less* provoked by a motivating CS+ stimulus, resulting in a diminished PIT effect. Moreover, the reduced provocation appeared to take place over the course of the Transfer phase instead of right away, which suggests a change in control strategies. We hypothesized that individuals with high RED are less able to reactively suppress responses, and therefore shift to a safer, more proactive strategy over the course of the Transfer phase. In subsequent analyses, we probed this "proactive" hypothesis with the

same trial-by-trial analysis used in Chapter 2. We found that individuals with low RED show the same trial-by-trial effects as we previously observed: a strong CS+ provocation following nogoCS- trials, yet no CS+ provocation following nogoCS+ trials. However, individuals with high RED are not provoked by the CS+ following nogoCS+, nor are they provoked after nogoCS- trials. These results suggest that high RED individuals use proactive control more often than low RED individuals, particularly as the experiment progressed.

In Chapter 4, I shift the focus back to the activation-suppression dynamic suggested by the results in Chapter 1. Using a variant of the go-nogo/PIT task with monetary rewards (which helped the motivational provocation not fade over time), we found that participants pressed faster on high compared to low reward trials. Participants also made more nogo errors on high reward trials, consistent with the results in Chapters 1 and 2. The TMS data show that, in support of our hypothesized activation-suppression model, high reward trials generate a strong early activation (within 150 ms after stimulus onset), which is followed by a sharp reduction in motor activity on nogo trials (most likely reflecting motoric suppression). We also found a close relationship between the activation and reduction phases, such that the strength of the reduction phase depends on the strength of the preceding activation, and that the activation-reduction dynamics are more pronounced in more motivated participants (assessed via overall RTs). Even more, we discovered that the TMS data predicted the amount of nogo errors participants made, but only when using a measure that takes both the activation and reduction phases into account. To verify that the reduction in motor activity reflects a top-down control process, we conducted a separate behavioral experiment that examined changes in nogo error rates

with and without mental fatigue. We found that nogo error rates only increased when participants were mentally fatigued, and that this increase was significantly greater for high versus low reward nogo trials. We interpret this as evidence that high reward nogo trials require significant top-down control, which is reflected in a steeper reduction of motor activity.

Finally, in Chapter 5, we extended our research on control over motivational provocations to a different type of real-world provocation, called motor affordances. These occur when the visual properties of an object elicit behaviorally relevant motor representations (Gibson, 1979). For example, viewing a right-facing cup handle activates left hemisphere motor areas (Chao & Martin, 2000; Grafton, Fadiga, Arbib, & Rizzolatti, 1997), resulting in potentiation of the right hand (McBride, Boy, Husain, & Sumner, 2012). We tested the hypothesis that the frontal cortex helps ensure that irrelevant affordance provocations remain below the threshold for actual movement. We therefore "loaded" the frontal cortex with an effortful working memory (WM) task (which ostensibly consumes frontal resources) while task-irrelevant affording objects appeared every so often. Using electrophysiological measures of motor affordances, we found typical affordance signatures under low WM load. However, under high WM load, the affordance was completely diminished. To probe further, we conducted a follow-up experiment and investigated the underlying mechanism responsible for the diminished affordance. This experiment showed that, under high WM load, there is greater inhibition in primary motor cortex. We postulate that this inhibitory activity prevents the affordance from potentiating the motor system. This suggests that the occurrence of provocations

depends on the excitatory/inhibitory state of the motor system at the time when the stimulus is viewed (Knight et al., 1999).

Response suppression over a motivationally driven provocation

The majority of response suppression research has used "cold" cognitive psychology tasks (e.g., stop-signal and go/nogo) that generate action tendencies by making the "go" signal occur much more frequently than the "stop" or "nogo" signal (e.g., 80%--go; 20%--nogo). In turn, participants expect to initiate a response at the beginning of each trial, and must then stop the action once the stop-signal or nogo cue is processed. In our go-nogo/PIT task, the proportion of go and nogo trials is equal; therefore, participants do not anticipate a "go" response before each trial. Instead, the action tendency is driven by the motivational significance of the background stimulus. This is captured by the MEP data in Chapters 1 and 4, which only reveal a strong early provocation when the background is a CS+ or a high reward stimulus. It is also captured in the behavioral satiation experiment in Chapter 1, where we found that the CS+ provocation does not occur when participants are satiated and not motivated to consume the juice reward. This indicates that response suppression is only triggered (or at least triggered to a greater degree) on CS+/high reward trials when participants are motivated to receive the reward. Thus, response suppression is not merely triggered by the nogo cue, but rather the conflict that emerges between the motivationally driven activation and the nogo cue. This dynamic resembles conflict tasks such as the Simon and flanker tasks, which only recruit response suppression on incongruent trials (Klein, Petitjean, Olivier, & Duque, 2013; van Campen, Keuken, Wildenberg, & Ridderinkhof, 2013). However, the

provocation in those tasks rarely has any motivational component, instead relying on learned or inherent automatic tendencies. As such, the underlying neural circuitry of the provocation is likely distinct, with the motivationally driven provocations being more strongly driven by dopaminergic bursts in the mesolimbic pathway (Beierholm et al., 2013; Bromberg-Martin, Matsumoto, & Hikosaka, 2010; Kelley & Berridge, 2002; Li et al., 2015). Importantly, the distinct provocation raises the possibility that the neural mechanism underlying response suppression over the provocation may also be somewhat distinct.

One piece of evidence that the suppression we observed is distinct from basic response control tasks concerns the specificity of the suppression. Whereas many studies have found that stopping (or withholding) an action has global effects on the motor system (Greenhouse, Oldenkamp, & Aron, 2012; Majid, Cai, George, Verbruggen, & Aron, 2012; Wessel, Reynoso, & Aron, 2013), we found evidence that withholding a motivationally driven action is selective to the task-relevant effector. This was evident in the MEP data in Chapters 1 and 2, which both found suppression selective to the task-relevant index finger. I therefore postulate that suppressing a motivationally driven action tendency is mediated by a different mechanism than the "hyperdirect" pathway generally observed in classic stop-signal and go/nogo tasks (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Aron, 2007; Chambers, Garavan, & Bellgrove, 2009). Instead, I surmise that it is mediated by the "indirect" pathway involving cortico-striatal circuitry. This is consistent with previous studies that have found evidence for a striatally-mediated system during selective stopping (Majid, Cai, Corey-Bloom, & Aron, 2013; Zandbelt, Bloemendaal, Neggers, Kahn, & Vink, 2013).

Reactive versus proactive response suppression: a crucial distinction

Previous response suppression research has made an important distinction between reactive and proactive suppression (sometimes called "inhibition"). Whereas reactive suppression is triggered once sufficient activation is generated, proactive suppression occurs when individuals suppress a particular effector in advance. In turn, this can help prevent an impending action tendency from ever taking place. Proactive suppression may be particularly helpful when the activation of a particular response is likely to hurt performance. For example, if a participant knows that there is a high likelihood that an imminent action tendency will need to be stopped, then proactively suppressing that finger in advance may be a more optimal strategy (Cai, Oldenkamp, & Aron, 2011).

In the current dissertation, we found that distinguishing between reactive and proactive suppression is also important when dealing with motivationally driven provocations. In Chapters 1 and 4, we show that motivationally driven provocations activate the motor system very quickly, and that the activation is subsequently suppressed once the nogo signal conflicts with the activation—making it a "reactive" process. This interpretation is substantiated by the close relationship observed between the activation and suppression phases (greater suppression follows greater activation).

In contrast to reactive suppression, we saw in Chapter 2 that participants can implement proactive suppression in the same go-nogo/PIT task, depending on what type of trial they just experienced. More specifically, if participants just experienced a "dangerous", high-conflict nogoCS+ trial, then they engage proactive suppression prior to the next trial. Interestingly, only the CS+ stimulus is affected on the next trial, suggesting

that proactive suppression is put in place to prevent a potentially inappropriate CS+ provocation. While the cause of the proactive suppression is still unclear, a reasonable hypothesis is that nogoCS+ trials raise participants' awareness of (or focus on) the potential "danger" of being provoked by a CS+ stimulus. As mentioned above, one effective way to prevent such a scenario is to proactively suppress the task-relevant effector and keep it suppressed if a CS+ occurs. Only when it becomes a certainty that "going" is appropriate does the suppression mechanism get released. This interpretation is based on the data from four experiments that analyzed these trial-by-trial effects, and we present our interpretation in a "proactive" model at the end of Chapter 2. It is also consistent with previous studies that have found selective suppression in a task-relevant effector prior to responding, often referred to as "impulse control" (Bestmann & Duque, 2015; Duque, Lew, Mazzocchio, Olivier, & Richard, 2010).

In Chapter 3, we postulate that this "proactive" account helps explain the slowing of the CS+ reaction times observed in the high reward eating drive (RED) group. However, instead of the proactive suppression only occurring after nogoCS+ trials, it appears that high RED individuals implement proactive suppression (or at least proactive control) after nogoCS- trials as well. We hypothesize that this increased use of proactive control may be due to a reduced ability to reactively suppress a motivated action tendency, though this hypothesis has yet to be confirmed. If true, then suppressing the response in advance (i.e. proactively) in an attempt to prevent the CS+ provocation from occurring would likely be the better, safer control strategy.

Self-control in the real world

Traditional response control tasks use stimulus-response pairings to generate action tendencies that must sometimes be controlled. However, this type of activation has limited applicability to the types of provocations people are most concerned about, such as unhealthy foods and drinks, drugs, sexual enticements, and gambling. Thus, we believe that the go-nogo/PIT paradigm, which elicits motivationally driven provocations, is better suited to extend response control findings to real-world self-control. We also find that proactive response suppression, which has been studied far less than reactive response suppression, plays a key role in self-control. This is an important point because a great deal of real-world self-control is probably done proactively. For example, dieters often know in advance that they are about to enter a location with food temptations that are incongruent with their long-term goal of losing weight. In these situations, they can ostensibly use proactive suppression to mitigate or prevent harmful provocations—which we found some evidence for in Chapters 2 and 3.

While the go-nogo/PIT paradigm may improve upon the applicability of response control paradigms, we acknowledge that it does not capture all of the important elements of real-world self-control. One of these elements is the tonic nature of most real-world self-control. For example, if a smoker sees a box of cigarettes on the table, self-restraint is only effective if it takes place over an extended period of time. Even minor moments of weakness can lead to dramatic failures in self-control. Thus, future studies would benefit from developing tasks that can induce strong motivational provocations over extended periods of time. This would allow a systematic investigation of how long individuals

could voluntarily suppress a motivated action tendency and what happens when the suppression is briefly lifted.

Outstanding issues

This dissertation provides a foundation for the role of response suppression in controlling motivationally driven action tendencies. However, from this work, several interesting and important questions have emerged that warrant exploration in future studies. First, in Chapter 1, we found that response suppression helps mitigate motivationally driven action tendencies via a mechanism that is selective to the task-relevant effector. Yet, it is unclear what the mechanism is. Based on previous studies investigating selective suppression, I postulated that suppressing a motivationally driven action tendency—at least in the go-nogo/PIT paradigm—recruits the "indirect" pathway. Another intriguing possibility is that the suppression is targeted at ventral limbic regions integral to the motivational drive, such as the ventral striatum and ventral tegmental area. Future work could use functional neuroimaging to help disentangle these possibilities.

A second open question involves the observation that individuals prevent future provocation via proactive suppression. While Chapter 2 establishes that controlling provocations this way is possible, it is not clear if participants did this in a voluntary, top-down manner. Instead, it may be that the reactive suppression exerted on nogoCS+ trials "carried over" to the next trial. One way to disentangle this would be to examine the trial-by-trial effects with several inter-trial intervals spread out over several seconds. If the suppression is merely "carried over" to the next trial, one might predict that it decays over a short period of time; otherwise, the ITI length should have no real influence.

Distinguishing between these accounts is important because showing that participants can *voluntarily* "boost" proactive control to prevent future provocations has considerable practical implications.

Another open question concerns the results from Chapter 3, which suggest that individuals with high reward eating drive engage proactive control more than individuals with low reward eating drive. We hypothesized that this would be especially important if they have deficient reactive control abilities. However, this is an untested assumption that requires further study. Moreover, because we did not use neurophysiological measures in this study, it is difficult to definitively know if proactive suppression per se was involved. For example, participants could have proactively focused more on the center of the screen to minimize processing of the Pavlovian stimulus in the background.

A final question stems from the finding in Chapter 5 that affordances are diminished during high cognitive load, most likely due to an increase of inhibitory activity in primary motor cortex. However, it is remains unclear if the same effects would emerge if participants were not concerned about being provoked while in a high load state. If an affordance emerged in this scenario, it would suggest that participants proactively amplify inhibitory activity in anticipation of a provoking object during high load. On the other hand, if the affordance was still diminished, then it would suggest that greater inhibitory activity is a byproduct of being under high WM load. Both possibilities have practical implications. Under the former scenario, individuals could alter inhibitory activity in motor cortex to prevent provocations in a top-down manner. If this is true of affordance-related provocations, then it may also be true of motivationally driven provocations. Under the latter scenario, individuals could reduce unwanted provocations

by engaging in a task that requires considerable energy and WM resources. However, our results from Chapter 4 suggest that once this WM task is no longer engaged, individuals might be *less* able to control inappropriate provocations. This highlights the need for further exploration into how motivational provocations and cognitive load interact with one another.

Conclusion

The current dissertation shows that both reactive and proactive response suppression play a pivotal role in controlling motivationally driven action tendencies. Importantly, it suggests that the control process relies on many factors, including the strength of the activation, recent "high conflict" exposures, motivational drive, mental fatigue, and the current state of the motor system. These results provide a foundation for when and how response suppression is recruited in the face of real-world provocations. It is my hope that future work will expand on these findings and further connect experimental research with real-world applications.

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