PAST SUBSTANCE USE DISORDER IS ASSOCIATED WITH A MORE RAPID TRANSITION FROM GOAL-DIRECTED TO HABITUAL RESPONDING

Theresa H. McKim

A thesis submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master of Arts in the Department of Psychology (Behavioral Neuroscience)

Chapel Hill
2014

Approved by:
Charlotte A. Boettiger
Daniel J. Bauer
Donita L. Robinson
Theresa H. McKim: Past substance use disorder is associated with a more rapid transition from goal-directed to habitual responding
(Under direction of Charlotte A. Boettiger)

The hallmark behavior of addiction is continued drug use despite serious negative consequences of such use. Animal research suggests that chronic drug use promotes an overreliance on habit-based behaviors at the expense of flexible goal-directed actions. However, an imbalance in these behavioral control systems has not been experimentally investigated in humans with a drug use history who are currently abstinent. The aim of this research study was to assess stimulus-response (S-R) learning and replacement to evaluate habitual versus goal-directed response selection in individuals with a substance use disorder (SUD) history. A total of 22 individuals with an SUD history and 30 healthy control subjects were tested in an S-R learning task to measure group differences in learning over time during pre-and post-devaluation phases of the task. Additionally, we examined perseverative responding after devaluation to assess the ability to adapt both well-established and recently learned S-R associations. We used multilevel modeling to analyze differences between groups in learning behavior over time. The results of this study provide evidence for habitual responding in the SUD history group relative to the control group. These habit-based behaviors were reflected by an increase in perseverative responding that persisted over time in the SUD history group. This is the first human study to provide evidence for an imbalance between habitual and goal-directed control in a learning task in which SUD individuals are not globally impaired, but where deficits in response selection are selective to inflexible habit-based responding.
ACKNOWLEDGEMENTS

I would like to express my sincerest gratitude to my mentor, Dr. Charlotte Boettiger for her guidance and knowledge throughout the course of this study. Additionally, I would like to thank Dr. Dan Bauer for his technical assistance and guidance with data analysis and Dr. Donita Robinson for her encouragement and thoughtful discussion. Additionally, I would like to thank my numerous research assistants for their help with data collection and organization, as well as my colleagues within the CABLab for their encouragement and support.
# TABLE OF CONTENTS

LIST OF TABLES........................................................................................................................................ vii

LIST OF FIGURES ......................................................................................................................................... viii

LIST OF ABBREVIATIONS........................................................................................................................... ix

Chapter 1: Introduction............................................................................................................................ 1

Chapter 2: Materials and Methods ......................................................................................................... 7
  Participants ................................................................................................................................................. 7
  General Procedure ................................................................................................................................. 7
  Data Analysis ........................................................................................................................................... 9

Chapter 3: Results .................................................................................................................................... 13
  Demographic and Psychometric Data ................................................................................................. 13
  Behavioral Performance during Training ............................................................................................ 13
  Model 1: Initial Performance Model without SUD Status ................................................................. 14
  Model 2: Final Performance Model with SUD Status ....................................................................... 15
  Perseverative Behavioral Indices ....................................................................................................... 16
  Model 1: Initial Perseverative Model without SUD Status ............................................................... 16
  Model 2: Final Perseverative Model with SUD Status .................................................................... 16

Chapter 4: Discussion ............................................................................................................................ 18
LIST OF TABLES

Table 1. Sample Demographics and Psychometric Data ......................................................... 32

Table 2. Fixed Effect Estimates (Top) and Variance-Covariance Estimates (Bottom) for Models of the Predictors of Learning Behavior ................................................................. 33

Table 3. Fixed Effect Estimates (Top) and Variance-Covariance Estimates (Bottom) for Models of the Predictors of Perseverative Behavior ......................................................... 34
LIST OF FIGURES

Figure 1. Predicted accuracy over time for FAM (red) and NOV (green) sets by group prior to devaluation.................................................................35

Figure 2. Predicted accuracy over time for FAM (red, top) and NOV (green, bottom) sets by group pre- and post-devaluation.................................................................36

Figure 3. Percentage of perseverative errors by group during the post-devaluation phase.................................................................37

Figure 4. Predicted perseverative errors over time for FAM (red) and NOV (green) sets by group post-devaluation.................................................................38
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>DLPFC</td>
<td>Dorsolateral prefrontal cortex</td>
</tr>
<tr>
<td>DLS</td>
<td>Dorsolateral striatum</td>
</tr>
<tr>
<td>DMS</td>
<td>Dorsomedial striatum</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorder – Fourth Edition</td>
</tr>
<tr>
<td>FAM</td>
<td>Familiar response set</td>
</tr>
<tr>
<td>IL</td>
<td>Infralimbic cortex</td>
</tr>
<tr>
<td>IQ</td>
<td>Intelligence quotient</td>
</tr>
<tr>
<td>LCD</td>
<td>Liquid crystal display</td>
</tr>
<tr>
<td>MINI</td>
<td>Mini International Neuropsychiatric Interview</td>
</tr>
<tr>
<td>MLM</td>
<td>Multilevel modeling</td>
</tr>
<tr>
<td>NOV</td>
<td>Novel response set</td>
</tr>
<tr>
<td>OCD</td>
<td>Obsessive compulsive disorder</td>
</tr>
<tr>
<td>OFC</td>
<td>Orbitofrontal cortex</td>
</tr>
<tr>
<td>PFC</td>
<td>Prefrontal cortex</td>
</tr>
<tr>
<td>S-R</td>
<td>Stimulus-response</td>
</tr>
<tr>
<td>SUD</td>
<td>Substance use disorder</td>
</tr>
<tr>
<td>TMS</td>
<td>Transcranial magnetic stimulation</td>
</tr>
<tr>
<td>UNC</td>
<td>University of North Carolina</td>
</tr>
<tr>
<td>Yrs</td>
<td>Years</td>
</tr>
</tbody>
</table>
Chapter 1: Introduction

Associative learning allows efficient interaction with our environment by using our previous experiences to adapt response selection. Initial associations between stimuli and responses are formed by goal-directed actions shaped by contingent outcomes of behavioral responses (Dickinson, 1985). These adaptable behavioral responses allow behavioral flexibility in response to changes in outcome value to maximize rewards obtained. Facilitation of behavioral autonomy occurs with repeated practice, thus leading to behaviors driven by stimulus-response (S-R) associations as opposed to action-outcome associations (Dickinson, 1985). Formation of S-R associations results in habit-based behaviors that are no longer under the control of an outcome or goal, and are instead stimulus-bound. The utility of both goal-directed and habit-based associations and the ability to switch between these learning systems enables rapid and automatic responses to familiar stimuli and facilitates cognitive flexibility to adjust responses in novel contexts. However, habit-based actions underlie behavioral patterns that are difficult to change and, in the context of addiction, theoretically promote compulsive drug use and susceptibility to relapse.

Extensive animal research into the neural bases of goal-directed actions versus habit-based S-R responding demonstrates that each rely on distinct frontostriatal circuits. However, few human studies have used the canonical assays of devaluation and contingency degradation to assess the neural systems involved in learning (Ostlund and Balleine, 2008; Balleine and O’Doherty, 2010). By using these assays, decreased responding for an outcome is evident if behavior is goal-directed and under the control of the current value of the reward, whereas habitual behavioral responses persist due to a cached representation of the S-R-outcome
association that does not allow for updating changes in response value. While there is some existing research on human habit learning, the tasks employed to date limit the ability to study the neural processes governing the dynamic relationship between both goal and habit systems in learning over time. Prior human studies have measured immediate changes after devaluation, with little emphasis on measurement of within-subject change during adaptation of learned behaviors. Furthermore, evaluating multiple time points per person can extend our understanding of individual trajectory differences by producing growth curves that characterize the shape and rate of learning processes, which include both initial goal-directed behavior prior to and immediately after devaluation; this approach allows assessment of changes in the relative dominance of the neural systems that contribute to both goal-directed and habit-based behavioral output. Work from our lab using an S-R learning task (Boettiger and D'Esposito, 2005) demonstrates the utility of this task in measuring neural correlates of new S-R learning, S-R execution, and S-R “overwriting” processes, paralleling recent work in animals focused on the frontostratal circuitry necessary for goal-directed and habit-based responding during learning. The use of a task in humans that can capture and assess the continuum of the learning process over time provides the opportunity to probe behavioral and neural contributions of associative learning mechanisms within an individual, as well as to further test between-person variables (e.g. group status) that may contribute to differences in learning behavior.

The predominant view in the animal literature for decades was the idea that initial goal-directed behavior gradually transitioned into habit-based responding (Dickinson, 1985); however, research in both animals and humans has begun to broaden and update our understanding of the neural bases of these processes, showing that these parallel neural circuits can compete for behavioral control and ultimately interact in a precise temporal manner to control learning (Coutureau and Killcross, 2003; Daw et al., 2005; Yin et al., 2006; Tran-Tu-Yen et al., 2009; Daw et al., 2011; Fanelli et al., 2013). In particular, using an optogenetic approach in rodents, Smith & Graybiel (2013) showed that action selection is controlled through
the medial prefrontal (PFC), a brain area that acts as an arbitrator. The key role of the mPFC in the flexible control of habits was demonstrated by showing that new behaviors could replace established habits, with perturbation of the mPFC facilitating a switch between previously- and newly-learned behaviors (Smith et al., 2012). A handful of human neuroimaging studies have examined the neural basis of goal-directed versus habitual responding (Valentin et al., 2007; de Wit et al., 2009). Although these studies parallel findings from the animal literature, the role of the PFC in goal-directed versus habitual responding has typically been assessed separately. The assumption of relative independence of associative learning systems during performance does not adequately capture cognitive flexibility, demonstrating the importance of task selection and development to address these concerns. Additional human neuroimaging studies have highlighted the concurrent use of neural circuits underlying goal-and habit-based response learning, disentangling both differential and additive function within frontostriatal circuitry (Boettiger et al., 2004; Daw et al., 2011). These studies have implemented behavioral tasks that examine the interaction between goal-and habit-based brain circuits to account for parallel activation of both systems throughout training as opposed to sequential activation of habit circuitry as training progresses. The development of methods to assess habit learning in humans combined with a better understanding of the neural circuitry involved in healthy individuals has motivated investigation of aberrant functioning of these brain areas in pathological behavior.

To further our understanding of habitual behavior in pathological behaviors such as addiction, animal studies have demonstrated that extended cocaine use (Belin and Everitt, 2008; Zapata et al., 2010) or alcohol use (Dickinson et al., 2002; Corbit et al., 2012; DePoy et al., 2013) promotes habitual behavior, as evidenced by stimulus, and not outcome, control of behavior. Moreover, the study by Corbit et al. (2012) found that insensitivity to outcome devaluation does not result from overtraining for sucrose reward unless animals are also exposed to alcohol. Together, these data suggest that exposure to drugs of abuse potentiates
habitual responses and that extended substance abuse alters the circuits underlying S-R learning and replacement.

In contrast to the variety of experimental paradigms used to produce habitual responding in animal models, success in translating these paradigms to human subjects has been modest. The clinical application of studying compulsive drug use cited by many (Hogarth et al., 2013) has been met with limited success in human experimental methods. Behavioral studies in humans using outcome devaluation have shown goal-directed behavior to obtain cigarettes in young adult smokers, suggesting that in a less severe dependence state there is hypervaluation of the drug reward where response selection is under the influence of the outcome and has not reached the opposite end of the continuum to become habitual (Hogarth and Chase, 2011; Hogarth, 2012). Additionally, non-contingent alcohol administration attenuated goal-directed control of food choice by rendering food selection insensitive to devaluation (Hogarth et al., 2012); these findings support the notion that exposure to drugs of abuse potentiates habit learning. Furthermore, a recent neuroimaging study in alcohol dependent patients demonstrated preferential habit-based responding during task performance at the expense of goal-directed behavior (Sjoerds et al., 2013). This is the first study to demonstrate the neural correlates of preferential habit-based responding in human addicts, although recruitment criteria indicated that participants were concurrently using psychoactive medications for depression and anxiety disorders, precluding the ability to attribute study outcome to alcohol use disorders. The studies in humans discussed above highlight the issues in measuring the acquisition of goal-directed versus habitual responding during experimental assessment of performance.

A major constraint in translating paradigms from animal models to human studies has been the selection of appropriate stimuli to elicit behavioral response selection. In an experimental laboratory setting, several studies have used food pictures to test goal-directed and habitual responding after training (de Wit et al., 2007). A direct issue with this method is
familiarity of cues in the natural environment and pre-exposure outside of the controlled lab setting. These issues represent pre-existing confounds that may account for individual differences in behavior that have not been adequately controlled for in human experimental studies. Additionally, several studies have used sensory specific satiety to test outcome devaluation, not only limiting the study sample to individuals presumed to enjoy these food options or drinks prior to study participation (e.g. fritos or chocolate), but also presenting an opportunity for previous taste aversion learning to accompany devaluation manipulations as well (Tricomi et al., 2004). As a control for these confounds, our task uses novel stimuli that can equate individuals on these factors that may bias learning. Moreover, previous studies of S-R learning in humans have been limited to simple one-to-one mapping of stimuli onto an equal number of manual response options (Deiber et al., 1997; Toni et al., 2001). Humans learn these associations very quickly, limiting their use for examining learning over time that requires higher order cognitive functions, including working memory faculties of the PFC. The task used in our behavioral study in individuals with a history of a substance use disorder (SUD) and control subjects measures both acquisition and execution of S-R learning over multiple time points to extend our understanding of habitual versus goal-directed response selection in humans. This research is critical to understanding whether general differences in S-R replacement ability occur in SUDs, as such deficits could hinder attempts to change habit-based responses to drug stimuli during recovery from addiction and thus promote relapse. Furthermore, findings from studies in addiction will promote testing of novel interventions designed to improve flexible control over response selection and potential identification of an intermediate phenotype for SUDs to help identify individuals at risk, ultimately improving SUD prevention.

We hypothesize that, relative to control subjects, people with an SUD history will show an enhanced capacity to acquire new S-R associations and an impaired ability to replace habitual responses. We further predict that individuals with an SUD history will display perseverative behavior when attempting to change S-R associations, quantified by errors in
responding that occurs when failing to update response selection. Using data collected from an fMRI-compatible S-R learning task (Boettiger and D'Esposito, 2005) as a first step toward our ultimate goal of uncovering the neural bases of habitual response formation and replacement in addictive disorders, we tested S-R learning and replacement to evaluate habitual versus goal-directed response selection in control participants and in individuals with an SUD history. We applied multilevel modeling (MLM) to characterize the change in learning behavior over time, inter-individual and intra-individual variability in learning rate, and the contribution of SUD status to variability in learning trajectories.
Chapter 2: Materials and Methods

Participants

A total of 62 subjects were recruited from the University of North Carolina (UNC) at Chapel Hill and the surrounding community via advertisements. Subjects were recruited into one of two groups, based on whether they did (n=22 SUD) or did not (n=40 control subjects; CS) meet DSM-IV criteria for past drug or alcohol dependence in a structured clinical interview (Sheehan et al., 1998). SUD participants self-reported a minimum of 2 weeks of abstinence at the time of recruitment (M = 2 yrs ± 2.5 yrs). All subjects were healthy individuals 18-40 years old with no known history of neurological disorders, no current psychiatric diagnoses (n=5 SUDs met criteria for past depression) or psychoactive drug or medication use (excluding nicotine and caffeine), and reported an IQ within the normal range. Participants were screened for psychoactive drug use (Biotechnostix, Inc., Markham, ON), including alcohol (FC-10, Lifeloc Inc., Wheat Ridge, CO). Thirty-one additional participants were recruited, including 4 individuals meeting MINI criteria for a current psychiatric disorder, but were excluded from all analyses. Each subject provided written informed consent as approved by the UNC Office of Human Research Ethics.

General Procedure

Subjects participated in 2 sessions, with at least 1 night’s sleep between the first and second sessions (Boettiger and D’Esposito, 2005). Subjects were paid for their participation, including performance bonuses in the second (testing) session. During session 1, participants first underwent a structured clinical interview, and then completed a standard battery of questionnaires (see “Behavioral Inventories”), followed by behavioral training on the
computerized S-R learning task (see “Behavioral Task”). Learning was then tested during Session 2.

Behavioral Inventories

We administered a number of standard questionnaires to quantify factors that could impact our results. We quantified alcohol use behavior with the Alcohol Use and Disorders Identification test (AUDIT) (Saunders et al., 1993) and substance use behavior with the Drug Use Screening Inventory, Domain I (DUSI-I) (Tarter, 1990) and the Drug Abuse Screening Test (DAST) (Skinner, 1982). We calculated density of familial alcohol abuse using the Family Tree Questionnaire (FTQ) (Mann et al., 1985). Neuropsychological questionnaires included the Barratt Impulsivity Scale (BIS-11) (Barratt, 1994), the Beck Depression Inventory (BDI) (Beck and Steer, 1987), Rotter's Locus of Control scale (LOC) (Rotter, 1966), the State-Trait Anxiety Inventory (STAI) (Spielberger, 1985), the Thought Action Fusion scale (TAF) (Shafran et al., 1996) and the Antisocial Practices (APS) of the Minnesota Multiphasic Personality Inventory 2 (MMPI-2) (Butcher JN et al., 1990). Education and occupation were quantified with the Hollingshead Socioeconomic Status (SES) score (Hollingshead, 1975). We estimated IQ with the Shipley Institute of Living Scale (SILS) (Zachary, 1991).

Behavioral Task

The S-R learning task was implemented in E-Prime 2.0 (PST Inc., Pittsburgh, PA), and based on a previously described task (Boettiger and D'Esposito, 2005). Stimuli were presented on a color LCD screen, and subjects used a four-button keypad for manual response selection using the fingers of their dominant hand. Participants were given instructions and a brief familiarization prior to completing the training phase of the task. Briefly, participants viewed abstract visual stimuli displayed briefly (700 ms) on the screen that they learned, through trial and error, to associate with specific manual responses. During the first, training session, participants learned 2 sets of S-R rules (FAM) to a criterion of ≥ 90% accuracy. Participants then returned after ≥1 night’s sleep to complete the test session. In the second, testing session,
participants first demonstrated retention of the previously learned (FAM) associations, then the learning task began. In the learning task, blocks of the two FAM sets were interspersed with blocks composed of two new (NOV) stimulus sets, to measure new S-R learning, and blocks of a control condition, consisting of novel, unrelated stimuli; blocks consisted of 15 randomly selected stimuli from the relevant set. Following 6 “runs” of 15 blocks each (3 per block type), subjects were informed that the correct responses for 2 sets (one FAM and one NOV set) had changed (response devaluation). Participants then learned the new correct S-R associations through trial and error. This response devaluation manipulation allows us to quantify habitual responding when attempting to overcome both well-learned (FAM) and freshly learned (NOV) S-R associations. Moreover, including FAM and NOV sets in which correct responses do not change allows us to account for effects of time and of context change.

**Data Analysis**

Our main index of performance was number of correct responses out of total responses across the twelve runs (6 runs each, pre- and post-devaluation) of the task. Our data structure is composed of 48 repeated measures, consisting of 4 stimulus set types (2 FAM, 2 NOV) that are measured within person over the 12 time points. We also collected reaction time data in each trial, and were able to assess error types (perseverative button press, other incorrect button press) post-devaluation to determine behavioral adaptation strategies utilized by participants. To test the significance of across group comparisons for demographic and psychological variables, we used unpaired two-tailed t-tests for continuous measures and $\chi^2$ tests for categorical measures. All analyses include age and IQ as covariates. All data analyses were performed within SAS (Cary, NC).

**Multilevel Modeling Strategy**

To adequately characterize the behavioral performance in our S-R learning task, we derived a generalized linear mixed model of performance accuracy with a binomial distribution and logit link function. Our measurement of accuracy at multiple time points both pre-and post-
devaluation yields increased power to detect within-subject change, with particular emphasis on the ability to compare pre-and post-devaluation trajectories and capture changes in performance. This analytical approach was used to determine changes in task performance parameters by adding SUD status to our model.

Multilevel modeling aims to account for variance at different levels within nested data. The first level unit of analysis is time, with 6 performance time points each during the pre-and post-devaluation phases. The second level unit of analysis is the person, and we assessed performance by the number of correct responses relative to the total number of responses. The second level estimates capture between-person variance in the rate of change of learning over time. Predictor variables are categorized into Level 1 (time-specific) and level 2 (person-specific) predictors based on the data structure. The models discussed below estimate two kinds of effects: fixed and random effects. Two models are fit to the data, and compared through changes in the -2log-likelihood to determine whether the addition of group status as a parameter improves model fit. Results for the models can be found in Table 2; fixed effects are presented in the top part of the table and random effects parameters are listed at the bottom. Significant parameters are marked with an asterisk.

We used a generalized linear mixed model to examine the change in the slope (γ10) during performance throughout the S-R learning task prior to devaluation and changes in post-devaluation relative to pre-devaluation performance (γ20). The equation for this model can be found in Appendix 1. We centered the time variable at the sixth run to denote that the transition point would occur after this measurement; the intercept (γ00) is therefore interpretable as the expected value at the final time point that concludes learning of novel sets and execution of familiar sets (prior to devaluation). Additionally, to account for within-subject factors that we employed based on the task design, we added three additional variables to level 1 for our model. We were interested in testing decreases in the number of correct responses when
changing S-R associations, and therefore added a predictor to establish the drop-off ($\gamma_{30}$) in performance expected based on devaluation. To indicate that the stimulus set-type (FAM, NOV) varied across the task and that the correct response button changed post-devaluation, we created a variable to code for the set-type ($\gamma_{40}$) and a “newresponse” variable ($\gamma_{70}$) to predict performance based on whether the correct button response changed post-devaluation. In our task, response devaluation only occurred for one of each set type (1 FAM, 1 NOV), while the responses for the other FAM and NOV sets remained unchanged to control for general time and context effects.

We included age ($\gamma_{01}$) and IQ ($\gamma_{02}$) at level 2, and these predictors were grand mean centered prior to being added to the model, to make the intercept and results interpretable as an individual at the average age and IQ for parameter estimates. We fit an initial model without group status as a predictor at level 2, and then added group status ($\gamma_{03}$) in the second model to compute changes in the variance parameter estimates. The equation for this model can be found in Appendix 2. Model fit was assessed by comparing changes in the -2log-likelihood value between the two models that were fit. Additionally, we modeled 4 random effects: the intercept ($u_{0j}$), the pre-devaluation learning period ($u_{1j}$), the change in learning rate ($u_{2j}$) post-devaluation relative to pre-devaluation, and the drop-off ($u_{3j}$) in performance predicted to result from devaluation (Table 2).

To further characterize response selection after the post-devaluation manipulation, we fit a generalized linear mixed model to examine the change in the slope of incorrect, perseverative responses over time. The equation for this model can be found in Appendix 3. We defined perseverative errors as incorrect responses where participants selected the previously correct button as opposed to selecting a new button when response contingencies were changed post-devaluation. We centered the within-subject predictor of time ($\gamma_{10}$) as the first time point post-devaluation to make the intercept ($\gamma_{00}$) interpretable as the expected value of errors during initial
S-R replacement. At level 1 we also modeled the within subject factor of set-type ($\gamma_{20}$) (FAM, NOV). At level 2, we included the between subject factors of grand mean centered age ($\gamma_{01}$) and IQ ($\gamma_{02}$) and group status ($\gamma_{03}$). Model fit was assessed by comparing changes in the -2log-likelihood value between the two models that were fit. Random effects were estimated for both the intercept ($u_0$) and time ($u_{1j}$) variables (Table 3).
Chapter 3: Results

Demographic and Psychometric Data

Demographic questionnaire measures demonstrate that there were no significant differences between the SUD and CS group in terms of education, SES, gender or ethnicity (Table 1). The two groups did, however, differ in terms of age and estimated IQ, with significantly lower average IQ and higher average age for the SUD group relative to the CS group. Between groups there were also significant differences in substance and alcohol use, such that SUD individuals had higher scores on all measures, including a higher family history of alcohol abuse (FTQ density; all p's <0.001). Psychometric assessments demonstrated that the SUD group was more impulsive (BIS), had higher antisocial scores (MMPI), was more likely to display trait anxiety (STAI-trait), and tended to be more focused on negative consequences for oneself (TAF).

Behavioral Performance during Training

Subjects were required to reach a performance criterion of 90% accuracy for each set during the initial training session (FAM). The order of the sets was counterbalanced across participants and there were no significant differences in the order of sets administered based on group status, $\chi^2(1) = 0.40, p=0.53$. Training to criterion took ~ 25 min, resulting in no significant differences between groups (CS: 11 blocks; SUD: 9 blocks) on the average number of blocks (40 trials per block) to learn the first set, $F_{(3,56)}=0.67\ p=0.57$. Once a successful strategy was established, learning associative rules for the second set was always more rapid, and was not significantly different between groups (CS: 4 blocks; SUD: 4 blocks), $F_{(3,56)}=0.39\ p=0.76$. Prior to returning for the testing session, training performance between groups was equivalent.
Additionally, there were no significant differences between group in the amount of time between the initial training and testing study sessions ($t_{(60)}=1.09$, $p=0.28$).

**Model 1: Initial Performance Model without SUD Status**

A generalized linear mixed model with a binomial distribution to account for non-normally distributed data, with a logit link function to relate the linear predictor to the expected value of the response distribution, was specified to estimate the predicted number of correct responses out of total responses for each subject $i$ at each time point $j$. In our initial model we found no significant main effects of age or IQ (Table 2). During learning of NOV sets and execution of FAM sets prior to devaluation, we observed significant main effects of set-type ($t_{(2903)}=10.41$, $p<0.001$) and time ($t_{(2903)}=15.34$, $p<0.001$), and a significant interaction between set-type and time prior to devaluation ($t_{(2903)}=-11.78$, $p<0.001$), demonstrating that, as expected, participants showed a greater rate of performance improvement in the NOV sets relative to FAM sets. A significant change in performance is evident after devaluation ($t_{(2903)}=-8.19$, $p<0.001$), such that performance declines; this decline was specific to sets with devalued responses ($t_{(2903)}=-15.78$, $p<0.001$), requiring behavioral adaptation. Additionally, this drop-off effect is evident for FAM sets that change responses relative to NOV sets ($t_{(2903)}=5.45$, $p<0.001$), suggesting less difficulty in overcoming FAM associations relative to more recently learned S-R associations.

During the post-devaluation phase, we observed a significant change in the rate of learning ($t_{(2903)}=-6.79$, $p<0.001$), such that the rate of learning post-devaluation is shallower relative to pre-devaluation learning. This change in learning rate interacts with set-type ($t_{(2903)}=4.03$, $p<0.001$), with a smaller decrement in rate of change for FAM sets relative to NOV sets. This difference in the rate of learning post-devaluation also interacts with response manipulation ($t_{(2903)}=7.97$, $p<0.001$), such that there is a steeper rate of change in learning for sets that have a response change relative to those where responses remain the same. This suggests that the devaluation manipulation successfully impacted performance for sets that change response contingencies.
Model 2: Final Performance Model with SUD Status

Group status was entered at level 2 to capture between groups differences within the analysis. The fixed effects from this model indicate similar results as demonstrated previously in model 1; adding group status did not qualitatively change the initial observations that occur for control subjects.

There was no significant interaction between pre-devaluation change in performance slope and group status \((t_{(2892)}=0.67, p=0.50)\), indicating that SUD subjects perform FAM sets and learn NOV sets similarly to the CS group (Figure 1; Table 2). Additionally, SUD individuals were predicted to perform better on FAM sets overall \((t_{(2892)}=4.14, p<0.001)\). Overall, this suggests that SUD participants are not impaired at this task, and are predicted to perform slightly better at well-established (FAM) S-R execution.

Based on the absence of a drop-off by SUD interaction \((t_{(2892)}=-1.07, p<0.001)\), this effect is not selective to group status (Figure 2). In contrast to the CS group, SUD participants do not show a drop-off effect that is specific to FAM sets, \((t_{(2892)}=-0.87, p=0.39)\), nor is it selective for FAM sets that change responses \((t_{(2892)}=-1.38, p=0.17)\). Additionally, the drop-off by new response interaction is not significantly different between groups \((t_{(2892)}=1.02, p=0.31)\). Performance changes due to devaluation in the SUD group do not differ from the CS group. The change in the rate of learning post-versus pre-devaluation did not interact with SUD status \((t_{(2892)}=0.93, p=0.35)\). However, there were significant group differences in the rate of learning post-devaluation relative to pre-devaluation for FAM set types \((t_{(2892)}=-2.39, p=0.02)\) and changed response contingencies \((t_{(2892)}=-2.95, p=0.003)\), although the interaction between the change in rate of learning post- versus pre-devaluation, set-type, and new response is marginal \((t_{(2892)}=1.74, p=0.08)\). The addition of group status as a between-subjects predictor does improve the fit of the model, which is demonstrated in Table 2 when comparing the change in the -2log-likelihood, \(\chi^2(1)=71.59, p<0.001\). These results suggest that group status impacts performance both pre-and post-devaluation.
Perseverative Behavioral Indices

To further assess response selection post-devaluation, a one-way ANOVA between group for each set-type (FAM, NOV) indicated significant differences between groups for the overall percentage of perseverative errors for the FAM set-type. The SUD group made a higher percentage of perseverative errors during replacement of more well-established (FAM) S-R associations ($F_{(1,58)}=10.45, \ p=0.002$; Figure 3). In contrast, no significant differences between groups for overall percentage of perseverative errors were evident for replacement of more recently established, NOV associations ($F_{(1,58)}=2.18, \ p=0.146$; Figure 3). This indicates the habitual nature of FAM S-R associations in SUD participants.

Model 1: Initial Perseverative Model without SUD Status

To further examine perseverative responding over time, we used a generalized linear mixed model with a binomial distribution and logit link function to predict the ratio of perseverative errors to total errors during performance in the post-devaluation phase. We found no significant main effects of age or IQ (Table 3). Significant main effects of set-type and time indicated that the number of perseverative errors in the FAM condition was significantly higher relative to the NOV condition ($t_{(679)}=2.81, \ p=0.005$) and number of perseverative errors declined over time ($t_{(679)}=-5.37, \ p<0.001$). There was no set-type by time interaction ($t_{(679)}=0.33, \ p=0.75$).

Model 2: Final Perseverative Model with SUD Status

Group status was entered at level 2 to account for between group differences within our analysis. For control subjects, there was no significant difference in the number of perseverative errors between sets ($t_{(676)} = 1.29, \ p=0.20$) (Table 3). Additionally, the number of perseverative errors declined over time ($t_{(676)}=-4.42, \ p<0.001$) and there was no set-type by time interaction ($t_{(676)}=-0.80, \ p=0.42$), similar to the previously estimated model effects (Table 3).

The addition of group status did not result in a significant main effect of group ($t_{(58)}=0.61, \ p=0.55$) nor a set-type by group interaction ($t_{(676)}=1.56, \ p=0.12$). There was also no interaction between time and group in the rate of change of percentage of perseverative errors over time,
indicating perseverative errors for both FAM and NOV sets remained stable over time. We also observed no significant interaction between set-type and group with time, demonstrating that the percentage of perseverative errors for FAM and NOV associations show a similar rate of change in both the SUD and CS group, \( t(676)=1.43, p=0.15 \); Figure 4). The addition of group status as a between-subjects predictor does improve the fit of the model, which is demonstrated in Table 3 by direct comparison of the models based on the \(-2\log\text{-likelihood value}, \chi^2(1)=23.87, p<0.001\). These findings further illustrate the persistence of habit-based responding in the SUD group for FAM S-R associations that are evident in perseverative responding selective to well-learned (FAM) S-R associations.
Chapter 4: Discussion

To the best of our knowledge, this is the first study providing behavioral evidence for perseverative responding for habit-based actions, with no overall global impairments in S-R association learning, in abstinent individuals with a history of a SUD. We demonstrate that this S-R task can measure learning over time and utilizes a devaluation manipulation that can distinguish habit-based from goal-directed responding for S-R associations. We further provide evidence that our task allows an examination of changes within learning trajectories over time, at the individual level as well as between groups. The data support our first hypothesis that the SUD group was not impaired at new learning relative to controls; interestingly, they were slightly better at executing learned FAM associations that were predicted to be habit-based. Furthermore, we examined error types during response replacement following devaluation, demonstrating that the SUD group is impaired in overwriting well-established (FAM) associations. The SUD group was more likely to show an increase in the percentage of perseverative errors overall during the post-devaluation phase specific to FAM associations, and a persistent increase in percentage of perseverative errors for FAM sets that was less likely to decline over time post-devaluation. Taken together, the data suggest a greater propensity to acquire S-R associations in SUD history participants that result in perseverative responding specific to over-trained, habit-based (FAM) associations, ultimately making replacement of habit-based responses most difficult.

The observed habit-based nature of responding in the SUD group could be a consequence of drug use experience that results in changes of the neural circuitry mediating S-R behavior, or a predisposition that contributes to vulnerability of developing a SUD. The current
study cannot determine whether habit-based action selection is a pre-existing risk factor for the
development of addiction or whether this behavioral response strategy reflects a consequence
of extended drug use. A further limitation of our study includes the SUD sample studied.
Participants were recruited based on any history of drug or alcohol use, and therefore we are
limited in extending our findings to a specific drug class or alcohol. It is unknown whether
differences in poly-substance dependence history versus selective use of a particular drug type
may result in differences in S-R learning and perseverative behavior based on this study;
variation in disease severity may result in differences in perseverative responding. Finally, our
SUD study group was limited to individuals not currently using psychoactive medications or
actively seeking treatment. The use of pharmacotherapy treatment for SUDs may result in
decreases in perseverative responding over treatment associated with medication status. These
limitations point to future avenues of interest that will help parse differences in habit-based
responding in addiction.

Although the underlying neural bases of behavioral differences in S-R re-learning that
we observed among people with SUDs are unknown, several lines of evidence point to
differences in frontostriatal circuit function. First, neuroimaging studies of people with SUDs
have repeatedly reported abnormal functioning of the OFC and striatum (Olausson et al., 2007;
Park et al., 2010; Volkow et al., 2011; ersche et al., 2012; Konova et al., 2012). Second, the
DLPFC/mPFC also appears to play a critical role in cue-induced drug self-administration in
animal models of relapse (Jackson and Moghaddam, 2001; Feltenstein and See, 2008). Third,
in monkeys, prolonged cocaine intake profoundly impairs S-R re-learning (Jentsch et al., 2002).
These data suggest that chronic exposure to drugs of abuse may potentiate habitual responses
and further supports a role for extended substance use in altering the circuits underlying S-R
learning and replacement. Evidence that forming and replacing S-R associations depends on
intact functioning of frontostriatal connections (de Wit et al., 2012), together with the fact that
addiction is characterized by a profound difficulty in overcoming habitual responses, suggests
that atypical functioning in the circuits subserving S-R learning and replacement contribute to addictive behaviors.

Recent work aimed at understanding the role of the prefrontal cortex in goal-versus habit-based responding used transcranial magnetic stimulation (TMS) and biological assays of stress to show a relationship between working memory capacity requiring frontal brain regions and stress as important factors that underlie the contribution of goal-directed versus habit-based behavioral strategies. Smittenaar et al. (2013) demonstrated that disruption of the right DLPFC through TMS rendered performance habit-based, while disruption of the left DLPFC impaired goal-directed behavior in individuals with low working memory capacity. Working memory capacity has been further posited to relate to susceptibility of stress, such that acute stress attenuates goal-directed behavioral contributions in task performance (Otto et al., 2013). These results lend further support to previous literature demonstrating a stress-induced shift in behavior from goal-directed to habit-based responding (Schwabe and Wolf, 2010; Schwabe et al., 2011; Schwabe and Wolf, 2011), and highlights the potential underlying protective mechanism of working memory capacity. Understanding whether stress can potentiate habitual behaviors that may in turn promote drug use is important for identifying mechanisms that may predict relapse. Future work aimed at further delineating the factors within this relationship may have major implications in our understanding of treatment interventions for substance use disorders.

Our study in abstinent drug users demonstrates that perseverative responding to non-drug related stimuli is a behavioral index of habit-based behavior. The current results are in line with a hallmark of addictive behavior: inflexible drug use that is under control of a stimulus as opposed to the outcome, where drug use continues despite negative consequences. A better understanding of differences in the underlying neural circuitry of goal-directed and habitual behavior in addiction is warranted, given the current limited knowledge in humans. Additionally, these basic circuits are involved in many types of behavioral disorders, including OCD and
Parkinson’s disease, in which differences in habit-based versus goal-directed neural circuitry dominance contribute to behavioral symptomatology. Probing the neurobiological basis of these behaviors is fundamental to determining how the brain allows us to establish, maintain and change behaviors. Furthermore, the development of novel approaches to overcoming habitual behaviors would have wide implications for everyday life as well as conditions characterized by intractable habits.
APPENDIX 1: MODEL 1 – INITIAL PERFORMANCE MODEL WITHOUT SUD STATUS

Response Distribution: $y_{ij} \mid \mu_{ij} \sim BIN(\mu_{ij})$

Linear Predictor:

\[
\eta_{ij} = \beta_{0j} + \beta_{1j} \text{Trend1}_{ij} + \beta_{2j} \text{Changetrend}_{ij} + \beta_{3j} \text{Dropoff}_{ij} + \beta_{4j} \text{Novel}_{ij} + \\
\beta_{5j} \text{Trend1}_{ij} \times \text{Novel}_{ij} + \beta_{6j} \text{Dropoff}_{ij} \times \text{Novel}_{ij} + \beta_{7j} \text{Dropoff}_{ij} \times \text{NewResponse}_{ij} + \\
\beta_{8j} \text{Dropoff}_{ij} \times \text{Novel}_{ij} \times \text{NewResponse}_{ij} + \beta_{9j} \text{Changetrend}_{ij} \times \text{NewResponse}_{ij} + \\
\beta_{10j} \text{Changetrend}_{ij} \times \text{Novel}_{ij} + \beta_{11j} \text{Changetrend}_{ij} \times \text{Novel}_{ij} \times \text{NewResponse}_{ij} + r_{ij}
\]

\[
\begin{bmatrix}
\eta_{0j} \\
\eta_{1j} \\
\eta_{2j} \\
\eta_{3j}
\end{bmatrix} \sim N \left( \begin{bmatrix} 0 \\
\tau_{10} \\
\tau_{20} \\
\tau_{30}
\end{bmatrix}, \begin{bmatrix} \tau_{00} & \tau_{11} & \tau_{12} \\
\tau_{11} & \tau_{22} & \tau_{23} \\
\tau_{12} & \tau_{23} & \tau_{33}
\end{bmatrix} \right)
\]

Level 2:

$\beta_{0j} = \gamma_{00} + \gamma_{01} \text{Age} + \gamma_{02} \text{IQ} + u_{0j}$

$\beta_{1j} = \gamma_{10} + u_{1j}$

$\beta_{2j} = \gamma_{20} + u_{2j}$

$\beta_{3j} = \gamma_{30} + u_{3j}$

$\beta_{4j} = \gamma_{40}$

$\beta_{5j} = \gamma_{50}$

$\beta_{6j} = \gamma_{60}$

$\beta_{7j} = \gamma_{70}$

$\beta_{8j} = \gamma_{80}$

$\beta_{9j} = \gamma_{90}$

$\beta_{10j} = \gamma_{100}$

$\beta_{11j} = \gamma_{110}$
APPENDIX 1 (CONT.)

Link Function: \( \eta_{ij} = \text{logit}(\mu_{ij}) \)

Reduced form equation:

\[
\text{Accuracy}_{ij} = \gamma_{00} + \gamma_{01}\text{Age} + \gamma_{02}\text{IQ} + \gamma_{10}\text{Trend1}_{ij} + \gamma_{20}\text{changetrend}_{ij} + \gamma_{30}\text{dropoff}_{ij} + \gamma_{40}\text{Novel}_{ij} + \\
\gamma_{50}\text{Trend1}_{ij} \times \text{Novel}_{ij} + \gamma_{60}\text{dropoff}_{ij} \times \text{Novel}_{ij} + \gamma_{70}\text{dropoff}_{ij} \times \text{NewResponse}_{ij} + \\
\gamma_{80}\text{dropoff}_{ij} \times \text{Novel}_{ij} \times \text{NewResponse}_{ij} + \gamma_{100}\text{changetrend}_{ij} \times \text{Novel}_{ij} + \\
\gamma_{110}\text{changetrend}_{ij} \times \text{Novel}_{ij} \times \text{NewResponse}_{ij} + \mu_{0j} + \mu_{1j}\text{Trend1}_{ij} + \mu_{2j}\text{changetrend}_{ij} + \\
\mu_{3j}\text{dropoff}_{ij} + \epsilon_{ij}
\]
APPENDIX 2: MODEL 2 – FINAL PERFORMANCE MODEL WITH SUD STATUS

Response Distribution: \( y_{ij} \mid \mu_{ij} \sim BIN(\mu_{ij}) \)

Linear Predictor:

\[
\eta_{ij} = \beta_0j + \beta_{ij}Trend_{1ij} + \beta_{2j}Changetrend_{ij} + \beta_{3j}Dropoff_{ij} + \beta_{4j}Novel_{ij} + \\
\beta_{5j}Trend_{1ij} \times Novel_{ij} + \beta_{6j}Dropoff_{ij} \times Novel_{ij} + \beta_{7j}Dropoff_{ij} \times NewResponse_{ij} + \\
\beta_{8j}Dropoff_{ij} \times Novel_{ij} \times NewResponse_{ij} + \beta_{9j}Changetrend_{ij} \times NewResponse_{ij} + \\
\beta_{10j}Changetrend_{ij} \times Novel_{ij} + \beta_{11j}Changetrend_{ij} \times Novel_{ij} \times NewResponse_{ij} + r_{ij} 
\]

\[
\begin{bmatrix}
  u_{0j} \\
  u_{1j} \\
  u_{2j} \\
  u_{3j}
\end{bmatrix}
\sim N
\left(
\begin{bmatrix}
  0 \\
  0 \\
  0 \\
  0
\end{bmatrix},
\begin{bmatrix}
  \tau_{00} & \tau_{01} & \tau_{02} & \tau_{03} \\
  \tau_{10} & \tau_{11} & \tau_{12} & \tau_{13} \\
  \tau_{20} & \tau_{21} & \tau_{22} & \tau_{23} \\
  \tau_{30} & \tau_{31} & \tau_{32} & \tau_{33}
\end{bmatrix}
\right)
\]

Level 2:

\[
\beta_{0j} = \gamma_{00} + \gamma_{01} \text{Age} + \gamma_{02} \text{IQ} + \gamma_{03} \text{Group}_j + u_{0j} \\
\beta_{1j} = \gamma_{10} + \gamma_{11} \text{Group}_j + u_{1j} \\
\beta_{2j} = \gamma_{20} + \gamma_{21} \text{Group}_j + u_{2j} \\
\beta_{3j} = \gamma_{30} + \gamma_{31} \text{Group}_j + u_{3j} \\
\beta_{4j} = \gamma_{40} + \gamma_{41} \text{Group}_j \\
\beta_{5j} = \gamma_{50} + \gamma_{51} \text{Group}_j \\
\beta_{6j} = \gamma_{60} + \gamma_{61} \text{Group}_j \\
\beta_{7j} = \gamma_{70} + \gamma_{71} \text{Group}_j \\
\beta_{8j} = \gamma_{80} + \gamma_{81} \text{Group}_j \\
\beta_{9j} = \gamma_{90} + \gamma_{91} \text{Group}_j \\
\beta_{10j} = \gamma_{100} + \gamma_{101} \text{Group}_j \\
\beta_{11j} = \gamma_{110} + \gamma_{111} \text{Group}_j
\]
Link Function: $\eta_{ij} = \logit (\mu_{ij})$

Reduced form equation:

Accuracy$_{ij} = \gamma_{00} + \gamma_{01}\text{Age} + \gamma_{02}\text{IQ} + \gamma_{10}\text{Trend1}_{ij} + \gamma_{20}\text{changetrend}_{ij} + \gamma_{30}\text{dropoff}_{ij} + \gamma_{40}\text{Novel}_{ij} + \gamma_{50}\text{Trend1}_{ij} \times \text{Novel}_{ij} + \gamma_{60}\text{Dropoff}_{ij} \times \text{Novel}_{ij} + \gamma_{70}\text{Dropoff}_{ij} \times \text{Novel}_{ij} + \gamma_{80}\text{Dropoff}_{ij} \times \text{Novel}_{ij} + \gamma_{90}\text{changetrend}_{ij} \times \text{NewResponse}_{ij} + \gamma_{100}\text{changetrend}_{ij} \times \text{Novel}_{ij} + \gamma_{110}\text{changetrend}_{ij} \times \text{Novel}_{ij} \times \text{NewResponse}_{ij} + \gamma_{111}\text{Trend1}_{ij} \times \text{Novel}_{ij} + \gamma_{112}\text{Group}_j \times \text{Trend1}_{ij} + \gamma_{21}\text{Group}_j \times \text{changetrend}_{ij} + \gamma_{31}\text{Group}_j \times \text{dropoff}_{ij} + \gamma_{41}\text{Group}_j \times \text{Novel}_{ij} + \gamma_{51}\text{Group}_j \times \gamma_{50}\text{Trend1}_{ij} \times \text{Novel}_{ij} + \gamma_{61}\text{Group}_j \times \gamma_{60}\text{Dropoff}_{ij} \times \text{Novel}_{ij} + \gamma_{71}\text{Group}_j \times \gamma_{70}\text{Dropoff}_{ij} \times \text{NewResponse}_{ij} + \gamma_{81}\text{Group}_j \times \text{Dropoff}_{ij} \times \text{NewResponse}_{ij} + \gamma_{91}\text{Group}_j \times \gamma_{90}\text{changetrend}_{ij} \times \text{NewResponse}_{ij} + \gamma_{101}\text{Group}_j \times \text{changetrend}_{ij} \times \text{Novel}_{ij} + \gamma_{111}\text{Group}_j \times \gamma_{110}\text{changetrend}_{ij} \times \text{Novel}_{ij} \times \text{NewResponse}_{ij} + u_{0j} + u_{1j}\text{Trend1}_{ij} + u_{2j}\text{changetrend}_{ij} + u_{3j}\text{dropoff}_{ij} + r_{ij}$
APPENDIX 3: FINAL PERSEVERATIVE MODEL WITH SUD STATUS

Response Distribution: $y_{ij} \mid \mu_{ij} \sim BIN(\mu_{ij})$

Linear Predictor:

$\eta_{ij} = \beta_0 + \beta_{1j}Time_{ij} + \beta_{2j}Novel_{ij} + \beta_{3j}Time_{ij} \times Novel_{ij} + \epsilon_{ij}$

\[
\begin{bmatrix}
\epsilon_{0j} \\
\epsilon_{1j}
\end{bmatrix} \sim N\left(\begin{bmatrix}0 \\
0\end{bmatrix}; \begin{bmatrix}
\tau_{00} & \tau_{10} \\
\tau_{10} & \tau_{11}
\end{bmatrix}\right)
\]

Level 2:

$\beta_{0j} = \gamma_{00} + \gamma_{01}Age + \gamma_{02}IQ + \gamma_{03}Group_j + u_{0j}$

$\beta_{1j} = \gamma_{10} + u_{1j}$

$\beta_{2j} = \gamma_{20}$

$\beta_{3j} = \gamma_{30}$

Link Function: $\eta_{ij} = \text{logit}(\mu_{ij})$

Reduced form equation:

PerseverativeErrors$_{ij} = \gamma_{00} + \gamma_{01}Age + \gamma_{02}IQ + \gamma_{03}Group_j + \gamma_{10}Time_{ij} + \gamma_{20}Novel_{ij} +$

$\gamma_{30}Time_{ij} \times Novel_{ij} + u_{0j} + u_{1j}Time_{ij} + \epsilon_{ij}$
REFERENCES


Table 1. Sample Demographics and Psychometric Data

<table>
<thead>
<tr>
<th></th>
<th>SUD (n=22)</th>
<th>CS (n=40)</th>
<th>t(df)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>29 ± 6</td>
<td>24 ± 6</td>
<td>-2.65</td>
<td>0.01</td>
</tr>
<tr>
<td>IQ</td>
<td>99 ± 6</td>
<td>105 ± 6</td>
<td>4.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>15 ± 2</td>
<td>15 ± 2</td>
<td>0.40</td>
<td>0.69</td>
</tr>
<tr>
<td>Subject Hollingshead SES</td>
<td>34 ± 16</td>
<td>36 ± 13</td>
<td>0.52</td>
<td>0.60</td>
</tr>
<tr>
<td>Parent Hollingshead SES</td>
<td>49 ± 14</td>
<td>55 ± 13</td>
<td>1.79</td>
<td>0.08</td>
</tr>
<tr>
<td>Hollingshead SES</td>
<td>41 ± 12</td>
<td>46 ± 9</td>
<td>1.51</td>
<td>0.14</td>
</tr>
<tr>
<td>SILS-Total</td>
<td>63 ± 6</td>
<td>68 ± 4</td>
<td>2.99</td>
<td>0.004</td>
</tr>
<tr>
<td>SILS-Vocab</td>
<td>31 ± 4</td>
<td>34 ± 3</td>
<td>2.66</td>
<td>0.01§</td>
</tr>
<tr>
<td>SILS-Abstract</td>
<td>32 ± 3</td>
<td>34 ± 3</td>
<td>2.34</td>
<td>0.02</td>
</tr>
<tr>
<td>Gender (# female)</td>
<td>10</td>
<td>20</td>
<td>ns†</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (# non-white)</td>
<td>6</td>
<td>17</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td><strong>Substance Use related</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUDIT Total</td>
<td>23 ± 10</td>
<td>4 ± 3</td>
<td>-8.60</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>AUDIT Consumption</td>
<td>8 ± 3</td>
<td>3 ± 2</td>
<td>-7.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AUDIT Dependence</td>
<td>6 ± 5</td>
<td>0.08 ± 0.35</td>
<td>-8.31</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>AUDIT Harm</td>
<td>8 ± 6</td>
<td>0.78 ± 1.33</td>
<td>-7.19</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>DAST</td>
<td>17 ± 7</td>
<td>1 ± 1</td>
<td>-10.79</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>DUSI-I (%)</td>
<td>0.80 ± 0.18</td>
<td>0.10 ± 0.12</td>
<td>-16.25</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>FTQ density (%)</td>
<td>0.41 ± 0.23</td>
<td>0.16 ± 0.22</td>
<td>-4.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Psychometric</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI</td>
<td>6 ± 6</td>
<td>3 ± 4</td>
<td>-1.69</td>
<td>0.10§</td>
</tr>
<tr>
<td>BIS Total</td>
<td>68 ± 15</td>
<td>55 ± 8</td>
<td>-3.61</td>
<td>0.001§</td>
</tr>
<tr>
<td>BIS Attention</td>
<td>18 ± 5</td>
<td>14 ± 3</td>
<td>-2.55</td>
<td>0.01</td>
</tr>
<tr>
<td>BIS Motor</td>
<td>25 ± 6</td>
<td>21 ± 3</td>
<td>-2.73</td>
<td>0.01§</td>
</tr>
<tr>
<td>BIS Non-planning</td>
<td>25 ± 6</td>
<td>20 ± 4</td>
<td>-4.31</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>LOC</td>
<td>8 ± 4</td>
<td>10 ± 3</td>
<td>1.99</td>
<td>0.051</td>
</tr>
<tr>
<td>MMPI-Antisocial</td>
<td>10 ± 5</td>
<td>6 ± 3</td>
<td>-3.57</td>
<td>0.001§</td>
</tr>
<tr>
<td>STAI Total</td>
<td>67 ± 15</td>
<td>60 ± 15</td>
<td>-1.63</td>
<td>0.11</td>
</tr>
<tr>
<td>STAI-State Anxiety</td>
<td>29 ± 7</td>
<td>27 ± 7</td>
<td>-0.96</td>
<td>0.34</td>
</tr>
<tr>
<td>STAI-Trait Anxiety</td>
<td>37 ± 9</td>
<td>33 ± 8</td>
<td>-2.02</td>
<td>0.048</td>
</tr>
<tr>
<td>TAF Total</td>
<td>19 ± 14</td>
<td>17 ± 13</td>
<td>-0.43</td>
<td>0.67</td>
</tr>
<tr>
<td>TAF Moral</td>
<td>15 ± 10</td>
<td>16 ± 11</td>
<td>0.40</td>
<td>0.69</td>
</tr>
<tr>
<td>TAF Self</td>
<td>3.0 ± 3.6</td>
<td>1.2 ± 2.1</td>
<td>-2.15</td>
<td>0.03§</td>
</tr>
<tr>
<td>TAF Others</td>
<td>1.4 ± 3.1</td>
<td>0.6 ± 1.6</td>
<td>-1.14</td>
<td>0.26§</td>
</tr>
</tbody>
</table>

Values are reported as mean ± standard deviation. Reported p-values reflect the results of unpaired two-tailed comparison between groups. SUD, History of substance use disorder subject; CS, Control subject; IQ, Intelligence Quotient; SES, Socioeconomic Status; AUDIT, Alcohol Use Disorders Identification Test; DAST, Drug Abuse Screening Test; DUSI-I, Drug Use Screening Inventory, Domain I; FTQ, Family Tree Questionnaire; BDI, Beck Depression Index; BIS, Barratt Impulsivity Scale; LOC, Locus of Control; MMPI, Minnesota Multiphasic Personality Inventory; SILS, Shipley Institute of Living Scale; STAI, State-Trait Anxiety Inventory; TAF, Thought Action Fusion Scale. **Boldface** indicates significant values. §p-value represents results from Satterthwaite method for unequal variances. †p-value represents results of χ² test. ns: p>0.05. #p-value represents result of Fischer’s exact test.
Table 2. Fixed Effect Estimates (Top) and Variance-Covariance Estimates (Bottom) for Models of the Predictors of Learning Behavior.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fixed effects</td>
<td>Fixed effects</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.95**(0.08)</td>
<td>0.91**(0.10)</td>
</tr>
<tr>
<td>Set</td>
<td>0.33**(0.03)</td>
<td>0.24**(0.04)</td>
</tr>
<tr>
<td>Trend1</td>
<td>0.23**(0.02)</td>
<td>0.23**(0.02)</td>
</tr>
<tr>
<td>Set×Trend1</td>
<td>-0.12**(0.07)</td>
<td>-0.12**(0.01)</td>
</tr>
<tr>
<td>Dropoff</td>
<td>-0.53**(0.07)</td>
<td>-0.48**(0.08)</td>
</tr>
<tr>
<td>Set×Dropoff</td>
<td>-0.01(0.10)</td>
<td>0.02(0.07)</td>
</tr>
<tr>
<td>Dropoff×NewResponse</td>
<td>-0.66**(0.04)</td>
<td>-0.69**(0.05)</td>
</tr>
<tr>
<td>Set×Dropoff×NewResponse</td>
<td>0.33*(0.06)</td>
<td>0.39**(0.07)</td>
</tr>
<tr>
<td>ChangeTrend</td>
<td>0.13**(0.02)</td>
<td>-0.15**(0.02)</td>
</tr>
<tr>
<td>Set×ChangeTrend</td>
<td>0.07**(0.02)</td>
<td>0.10**(0.02)</td>
</tr>
<tr>
<td>NewResponse×ChangeTrend</td>
<td>0.22**(0.01)</td>
<td>0.15**(0.02)</td>
</tr>
<tr>
<td>Set×NewResponse×ChangeTrend</td>
<td>-0.01(0.02)</td>
<td>-0.03(0.03)</td>
</tr>
<tr>
<td>Age (centered)</td>
<td>0.01(0.01)</td>
<td>0.01(0.01)</td>
</tr>
<tr>
<td>IQ (centered)</td>
<td>0.002(0.01)</td>
<td>0.01(0.01)</td>
</tr>
<tr>
<td>SUD</td>
<td>0.13(0.18)</td>
<td></td>
</tr>
<tr>
<td>Set×SUD</td>
<td>0.28**(0.07)</td>
<td></td>
</tr>
<tr>
<td>Trend1×SUD</td>
<td>0.02(0.03)</td>
<td></td>
</tr>
<tr>
<td>Set×Trend1×SUD</td>
<td>0.01(0.02)</td>
<td></td>
</tr>
<tr>
<td>Dropoff×SUD</td>
<td>-0.14(0.13)</td>
<td></td>
</tr>
<tr>
<td>Set×Dropoff×SUD</td>
<td>-0.11(0.13)</td>
<td></td>
</tr>
<tr>
<td>Dropoff×NewResponse×SUD</td>
<td>0.10(0.09)</td>
<td></td>
</tr>
<tr>
<td>Set×Dropoff×NewResponse×SUD</td>
<td>-0.17(0.13)</td>
<td></td>
</tr>
<tr>
<td>ChangeTrend×SUD</td>
<td>0.04(0.04)</td>
<td></td>
</tr>
<tr>
<td>Set×ChangeTrend×SUD</td>
<td>-0.09(0.04)</td>
<td></td>
</tr>
<tr>
<td>NewResponse×ChangeTrend×SUD</td>
<td>-0.09*(0.03)</td>
<td></td>
</tr>
<tr>
<td>Set×NewResponse×ChangeTrend×SUD</td>
<td>0.07(0.04)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variance of Random Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
</tr>
<tr>
<td>Trend1</td>
</tr>
<tr>
<td>ChangeTrend</td>
</tr>
<tr>
<td>Dropoff</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Correlations Between Random Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trend1/intercept</td>
</tr>
<tr>
<td>ChangeTrend/intercept</td>
</tr>
<tr>
<td>ChangeTrend/trend1</td>
</tr>
<tr>
<td>Dropoff/intercept</td>
</tr>
<tr>
<td>Dropoff/trend1</td>
</tr>
<tr>
<td>Dropoff/changeTrend</td>
</tr>
</tbody>
</table>

-2log-likelihood: 23,279.02, 23,208.47

Standard errors are in parentheses. Set denotes the familiar versus novel set-type variable, with novel set-type as the reference category. Trend1 indicates the slope of performance during pre-devaluation time points. Drop-off signifies the difference in performance pre-and post-devaluation. NewResponse indicates a change in the correct response as a result of devaluation. ChangeTrend is the variable denoting the change in post-devaluation performance relative to pre-devaluation performance. SUD, substance use disorder. The random parameters represent the variance and covariance estimates generated from inclusion of random effects in the model. The -2log-likelihood demonstrates the value for model fit. *p<0.05, **p<0.001.
Table 3. Fixed Effect Estimates (Top) and Variance-Covariance Estimates (Bottom) for Models of the Predictors of Perseverative Behavior

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed Effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.88**(0.06)</td>
<td>-0.91**(0.08)</td>
</tr>
<tr>
<td>Set</td>
<td>0.19*(0.01)</td>
<td>-0.17**(0.08)</td>
</tr>
<tr>
<td>Time</td>
<td>-0.11**(0.02)</td>
<td>-0.12**(0.03)</td>
</tr>
<tr>
<td>Set×Time</td>
<td>0.01(0.75)</td>
<td>-0.03(0.03)</td>
</tr>
<tr>
<td>Age (centered)</td>
<td>0.02(0.01)</td>
<td>0.02(0.01)</td>
</tr>
<tr>
<td>IQ (centered)</td>
<td>-0.01(0.01)</td>
<td>-0.01(0.01)</td>
</tr>
<tr>
<td>SUD</td>
<td>0.09(0.14)</td>
<td>0.22(0.14)</td>
</tr>
<tr>
<td>Set×SUD</td>
<td>0.02(0.04)</td>
<td>0.08(0.05)</td>
</tr>
<tr>
<td>Time×SUD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Set×Time×SUD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variance of Random Effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.10</td>
<td>0.09</td>
</tr>
<tr>
<td>Time</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Correlation Between Random Effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time/intercept</td>
<td>0.02</td>
<td>0.02</td>
</tr>
</tbody>
</table>

-2log-likelihood  2,961.35  2,937.48

Standard errors are in parentheses. Set denotes the familiar versus novel set-type variable, with novel set-type as the reference category. Time indicates the slope of performance during post-devaluation time points. SUD, substance use disorder. The random parameters represent the variance and covariance estimates generated from inclusion of random effects in the model. The -2log-likelihood demonstrates the value for model fit. *p<0.05, **p<0.001.
Figure 1. Predicted accuracy over time for FAM (red) and NOV (green) sets by group prior to devaluation. Solid lines represent the control group and dashed lines represent the SUD history group.
Figure 2. Predicted accuracy over time for FAM (red, top) and NOV (green, bottom) sets by group pre- and post-devaluation. Blue lines indicate sets for each set-type (FAM, NOV) that do not change response contingencies post-devaluation. Solid lines represent the control group and dashed lines represent the SUD history group.
Figure 3. Percentage of perseverative errors by group during the post-devaluation phase. NOV stimulus set is depicted in green and FAM stimulus set is depicted in red. Solid bars denote the control group and hatched bars denote the SUD history group. Error bars represent standard error of the mean.
Figure 4. Predicted perseverative errors over time for FAM (red) and NOV (green) sets by group post-devaluation. Solid lines represent the control group and dashed lines represent the SUD history group.