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Cocaine-specific speed-accuracy trade-off during anti-saccade testing differentiates patients with cocaine use disorder who achieve initial abstinence during treatment

Constanza de Dios, Ph.D.¹, Robert Suchting, Ph.D.¹, Heather E. Webber, Ph.D.¹, Jin H. Yoon, Ph.D.¹, Luba Yammine, Ph.D. ARPN¹, Jessica Vincent, B.S.¹, Michael F. Weaver, M.D.¹, Angela L. Stotts, Ph.D.², Joy M. Schmitz, Ph.D.¹, Scott D. Lane, Ph.D.¹

¹Center for Neurobehavioral Research on Addiction, Department of Psychiatry & Behavioral Sciences, UTHealth McGovern Medical School, University of Texas Health Science Center at Houston

²Department of Family and Community Medicine, UTHealth McGovern Medical School, University of Texas Health Science Center at Houston

Abstract

Background: The response time speed-accuracy trade-off (SATO) is an established index of information processing ability, but rarely examined as a variable in association with treatment of substance use disorder (SUD).

Aim: The purpose of this study was to test baseline information-processing ability differences between individuals who respond to treatment for cocaine use disorder versus those who do not.

Methods: Eighty patients enrolled in a clinical trial for cocaine use disorder completed a baseline drug-specific eye-tracking (anti-saccade) assessment prior to treatment, which included trials with both cocaine-related and neutral stimuli. SATO functions were computed for treatment responders vs. non-responders.

Results: Unexpectedly, responders demonstrated statistically different SATO functions, showing poorer accuracy when executing faster response times. This difference was present on trials that presented cocaine stimuli only.

Conclusions: SATO during performance of an eye-movement task may be useful for predicting differential response to substance use disorder treatment. However, in the present study, results were specific to cocaine cues rather than an overall SATO performance decrement.

Keywords

Cocaine Use Disorder; Anti-saccade; Eye Tracking; Speed-Accuracy Trade-off; Substance Use Treatment

Corresponding author: Constanza de Dios, Ph.D., Department of Psychiatry & Behavioral Sciences, UTHealth McGovern Medical School, 1941 East Road, Houston, TX USA 77054, phone: 713-486-2826, fax: 713-486-2618; Constanza.Inez.C.deDios@uth.tmc.edu.

Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

Introduction

Information processing speed serves as proxy for cognitive ability, reflecting the organization and efficiency of neural circuitry (Kuznetsova et al., 2016). Similarly, accuracy on speeded performance tests is believed to reflect cognitive ability and coherent neural organization, or the converse, neural dysfunction (Heitz, 2014). Among the first lawful relationships demonstrated in experimental psychology is the trade-off between response speed and performance accuracy, and modern accounts emphasize the importance of assessing the speed-accuracy trade-off (SATO) vs. accuracy alone to characterize cognitive functioning in speeded decision contexts (Heitz, 2014). SATO is commonly assessed as a conditional accuracy function (CAF), plotting accuracy against binned response speeds. CAFs increase monotonically under most experimental contexts. Choices made more rapidly result in more errors, and accuracy increases as response time (latency to execute a decision) increases. Accuracy asymptotes near a response-time threshold, posited to reflect full processing of relevant information prior to executing a decision. Group or individual differences in the slope of the CAF and deviations in accuracy at specific response speeds can indicate impairment in information processing and neural pathology (Haworth et al., 2016).

Dysfunctions in information-processing, assessed at both the neural and the cognitive performance level, are robustly connected to development, maintenance, and relapse in substance use disorder (SUD) (Jarmolowicz et al., 2013). Accordingly, cognitive enhancement could be a targetable mechanism for primary or adjunctive SUD treatment (Aharonovich et al., 2018; Rezapour et al., 2016). A large database demonstrates a range of associations between brain function, neurocognitive performance, and treatment outcomes and/or sustained abstinence in psychostimulant dependence (Aharonovich et al., 2006; Hanlon et al., 2013). Accordingly, over the past decade, cognitive enhancement has been suggested to facilitate recovery in psychostimulant use disorder. It should also be acknowledged that, to date, interventions targeted at enhancing cognitive functions have produced mixed results, either through pharmacological enhancement or computer-based cognitive training (Mahoney, 2019; Schulte et al., 2018; Sofuoglu et al., 2013; Verdejo-Garcia et al., 2019).

The present report highlights an effort to capitalize on the predictability and utility of the SATO as an index of information-processing capacity in SUD. The purpose of the current investigation was to test baseline differences in visual information-processing ability between individuals who subsequently respond to treatment for cocaine use disorder versus those who do not. CAFs were analyzed based on performance during a drug-specific anti-saccade task (Tannous et al., 2019). In an anti-saccade task, individuals are instructed to look in the opposite direction of a stimulus presented in the peripheral visual field. Demonstrating an accurate anti-saccade requires suppressing the reflexive orienting towards that stimulus and performing the rapid eye movement to the hemifield opposite the stimulus. Based on the association between cognitive function and treatment outcomes in psychostimulant use disorders, we hypothesized that CAFs would reveal differences between responders and non-responders following cocaine treatment. Specifically, we expected that non-responders would show lower SATO performance compared to responders. We also examined whether

SATO performances would differ between anti-saccade trials that presented cocaine vs. neutral stimuli.

Methods

This study was approved by the local UHealth IRB (HSC-MS-15-0595) in accord with the ethical principles of the Declaration of Helsinki and the Belmont Report. Eligible participants were treatment-seeking individuals who met current *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) criteria for cocaine use disorder (CUD) of at least moderate severity (4 symptoms). All participants (17 responders, 63 non-responders) signed written informed consent. Anti-saccade performance was obtained at baseline, prior to treatment. CUD participants were randomized to 4-weeks of either contingency management (CM) plus standard drug counseling or CM plus acceptance and commitment therapy (ACT). Both conditions included drug testing at thrice-weekly clinic visits. Participants were categorized as responders if they demonstrated sustained initial abstinence (i.e., 6 consecutive cocaine-negative urine samples in the first 4 weeks, set forth *a priori* as part of the adaptive design in Schmitz et al., 2014). Those who did not achieve initial abstinence or dropped out of the study were categorized as non-responders. After the initial 4-week treatment phase, patients were assigned to different medication conditions based on treatment response, using an adaptive SMART trial design (full study details available at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02896712): NCT 02896712). Data from the present experiment represent a sub-project examining eye-movements and information processing and were not a primary component of the NCT.

Baseline eye-tracking testing consisted of blocks of pro-saccade and anti-saccade trials using cocaine-specific or matched-neutral stimuli. To summarize, participants were tested with a 60-Hz infrared binocular eye-tracker. They performed four, 24-trial counterbalanced testing blocks (2 pro-saccade, 2 anti-saccade). Each 24-trial block included 12 cocaine- and 12 neutral- stimulus trials, presented randomly but with no trial type occurring on more than 3 consecutive trials. Blocks were separated by a 60 second rest period. Trials were separated by an intertrial interval averaging 600 ms (jittered between 350 and 750 ms to prevent anticipatory effects). Pro-saccade error rates were < ~3% across blocks. Low error rates on the pro-saccade task indicate no gross pathology to retinal nerves, visual cortex, or frontal eye fields, and that the participants are following instructions. Cocaine-related and neutral images were matched as closely as possible for color and complexity (see Dias et al., 2015; Tannous et al., 2019 for further experimental details).

Anti-saccade trial accuracy and response times were obtained from the raw data (pro-saccade trial errors were <2% for all participants). Response time was operationally defined as the latency to execute a saccade, where the position of the eyes exited the defined space around a centered on-screen fixation cross and entered the defined stimulus space, i.e., a rectangular on-screen space occupied by the picture (error) or directly opposite and the same size as the picture (correct anti-saccade). Based on the anti-saccade literature and suggested best practices, trials with latencies <90ms were considered anticipatory and excluded from analysis (Abel and Douglas, 2007; Tannous et al., 2019). Response times were then binned into the following percentiles: 10, 25, 50, 75, 90. A correct anti-saccade was defined as

an eye movement away from on-screen picture. Average anti-saccade accuracy for each response bin was determined to obtain CAFs for each participant via the R package *flankr* (Grange, 2016).

CAFs were analyzed using linear mixed-effects models via the R package *lme4* (Bates et al., 2015). Accuracy was the outcome measure, and each model tested for differences between groups (responder/non-responder), within repeated measures (response bins), and the group x response bin interaction. Age was included as a covariate due to (1) a marginal correlation with overall accuracy (see results), and (2) the established relationships between increased age and both increased anti-saccade error rates and slower reaction times (Abel and Douglas, 2007). Variance explained by the models was estimated using semi-partial R^2 (R_m^2), the proportion of variance explained by each fixed effect adjusted for other predictors (R package *r2glmm*, Jaeger, 2017). All models were initially run with therapy group as a covariate; however, because it did not significantly predict accuracy nor alter the reported effects in the linear mixed-effects models below, we do not further consider therapy group in the models. Significant group x response bin interactions were further examined through contrast tests of estimated marginal means (R package *emmeans*, Lenth, 2020). Because it is documented that participants with CUD show differential anti-saccade error rates and response times to cocaine vs. neutral stimuli (Tannous et al., 2019), and because the project had no aim to interpret CAFs with regard to 3-way interactions (group x response speed bin x stimulus type), data for cocaine stimuli were modeled separately from neutral stimuli.

Results

Participants (N=80) had a mean age of 50.36 ($SD=7.18$), and a mean education level of 12.67 (1.37) years. The sample was predominantly Black (79%) and included 65 males (12 responder, 53 non-responder) and 15 females (5 responder, 10 non-responder). Prior to the primary analyses and to minimize possible influences of the numeric imbalance between groups, sample characteristics (age, sex, race, education level, and therapy group) were examined as potential confounders of the relationship between responder group and the primary outcome variable, anti-saccade accuracy (Pocock et al., 2002). The responder and non-responder groups were not different on any sample characteristics (all $p>0.200$). Additionally, the potential confounds were not associated with anti-saccade accuracy, with the exception of age, which showed a marginal association ($p=0.065$). This observation aligns with existing literature and accordingly age was included as a covariate in the statistical models (Pocock et al., 2002; Tannous et al., 2019).

The first linear mixed model examined accuracy on cocaine-stimulus trials as the outcome measure ($R_m^2=0.354$). There was a significant main effect of response bin, $F(5,390)=35.40$, $p<0.001$, $R_m^2=0.312$. There was a significant response bin x group interaction, $F(5,390)=2.29$, $p=0.045$, $R_m^2=0.029$. Pairwise follow-up tests of the marginal means revealed that the responders had lower estimated marginal mean accuracy than non-responders at the three slowest response time bins: 0-10th percentile bin $t=2.32$, $p=0.021$ (accuracy=0.17 and 0.37, respectively, mean difference=0.192); 11-25th percentile bin $t=2.38$, $p=0.018$ (accuracy=0.21 and 0.40, respectively, mean difference=0.198); and 26-50th percentile bin $t=2.17$, $p=0.031$ (accuracy=0.32 and 0.50, respectively, mean

difference=0.180). These results are summarized in the left panel of Figure 1. Accuracy at the next three percentile bins did not differ between the groups ($p=0.942$, 0.437 , and 0.345). Age was not an independent predictor in the model ($p=0.098$).

The second linear mixed model examined accuracy on neutral-stimulus trials as the outcome measure ($R_m^2=0.261$). There was a significant main effect of response bin, $F(5,390)=18.22$, $p<0.001$, $R_m^2=0.189$. In contrast with the cocaine-stimulus trials, there was no significant group x response bin interaction ($p=0.919$), nor a main effect of group ($p=0.168$). These results are summarized in the right panel of Figure 1. Age was not an independent predictor in the model, but the p -value was marginal, $F(1,77)=3.81$, $p=0.055$, $R_m^2=0.047$.

Discussion

Cocaine treatment responders showed more compromised speed-accuracy tradeoffs vs. non-responders on a baseline, drug-specific anti-saccade task, but only on trials that presented cocaine stimuli. Measured as conditional accuracy functions, responders demonstrated significantly poorer accuracy when executing faster response times. These altered speed-accuracy functions are hypothesized to reflect compromised information-processing and neural organization (Heitz, 2014); similar patterns are observed in some neurological diseases (Haworth et al., 2016). These findings were unexpected within the framework of our initial hypothesis. The extant literature suggests cognitive impairment increases as a function of severity and/or duration of cocaine use (Aharonovich et al., 2006; Hanlon et al., 2013; Tannous et al., 2019; Verdejo-Garcia et al., 2019), and it follows that those participants with more compromised information processing capacity would have more difficulty achieving initial abstinence. Furthermore, these participants might be expected to display increased attentional bias to drug-relevant cues (Dias et al., 2015; Field et al., 2014). Our results were contrary to this expectation. In the subsequent discussion, we offer interpretation of the outcomes and note the study limitations.

Although the responder and non-responder groups were substantially uneven in number and such imbalance may normally present statistical issues, they would only pose a concern in the current study if baseline variables confounded the results. The results showed that assignment to therapy arm did not differ between responders and non-responders, and both groups were otherwise balanced on all baseline covariates, hence the primary question arises: why would those who subsequently demonstrated an initial treatment response (6 consecutive cocaine-negative urine samples) reveal impaired performance on the visual information processing (eye-tracking) test? Responders clearly made more anti-saccade errors on cocaine-stimulus trials when executing faster response speeds. Possibilities consistent with this evidence include differential information processing strategies or baseline impairment in neurocognitive functioning specific to this group. Given that the differential CAFs were observed on trials containing cocaine images, it is also likely that stimulus salience and attentional capture contributed to the observed results. There is insufficient information to speculate on why there may have been differential baseline salience between the groups, and counterintuitively why the responder group would display impaired SATO when faced with cocaine-cue trials. This raises the possibility that the results are spurious, an important issue underscored by recent observations that many

experiments in psychology fail to replicate (Open Science Collaboration, 2015). Ultimately, the preceding speculations can only be reconciled by direct or systematic replication, which we hope to undertake in future experiments.

This brief report is limited by a small N in the responder group and the absence of confirmation of CAF differences being supported by neuroimaging data. We also temper the above conclusions by noting that the observed effect sizes are modest and would thus call for further experiments with larger and (preferably) balanced responder vs. non-responder groups. Nevertheless, the present report can be interpreted as an intriguing observation worth consideration in follow-up work related to neurocognitive functioning in the context of SUD treatment outcomes (Aharonovich et al., 2006, 2018; Hanlon et al., 2013; Rezapour et al., 2016; Mahoney 2019). Associating differential SATO effects with neuroimaging data may offer further information in the way of underlying mechanisms.

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Figure 1.

Speed-accuracy trade-off on anti-saccade trials, shown as conditional accuracy functions for responder and non-responder groups. Accuracy is plotted on the y-axis as a function of response speeds binned by percentile (0-10, 11-25, 26-50, 51-75, 76-90, 91-100) on the x-axis. Data are plotted separately for cocaine stimuli (left panel) and neutral stimuli (right panel).