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Cortical paired associative stimulation shows impaired plasticity of inhibition networks as a function of chronic alcohol use

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Abbreviations:
AUD: Alcohol use disorder; ARLD: Alcohol-related liver disease; cPAS: Cortical paired associative stimulation; EEG: Electroencephalograph; EMG: Electromyograph; GABA: Gamma-aminobutyric acid; HC: Healthy control; ISI: Interstimulus interval; LTD: Long-term depression; LTP: Long-term potentiation; M1: Primary motor cortex; MEP: Motor-evoked potential; MNI: Montreal Neurological Institute; NMDA: N-methyl-D-aspartic; PAS: Paired associative stimulation; PFC: Prefrontal cortex; pre-SMA: Presupplementary area; rIFC: Right inferior frontal cortex; SSRT: Stop signal reaction time; SST: Stop Signal Task; SUD: Substance use disorder; TMS: Transcranial magnetic stimulation

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Abstract

Background. Response inhibition – or the ability to withhold a suboptimal response – relies on the efficacy of fronto-striatal networks, and is impaired in neuropsychiatric disorders including addiction. Cortical paired associative stimulation (cPAS) is a form of transcranial magnetic stimulation (TMS) which can strengthen neuronal connections via spike-timing-dependent plasticity mechanisms. Here, we used cPAS targeting the fronto-striatal inhibitory network to modulate performance on a response inhibition measure in chronic alcohol use.

Methods. Fifty-five participants (20 patients with a formal alcohol use disorder (AUD) diagnosis (26–74 years, 6[30%] females) and 20 matched healthy controls (HCs) (27–73 years, 6[30%] females) within a larger sample of 35 HCs (23–84 years, 11[31.4%] females) underwent two randomized sessions of cPAS 1-week apart: right inferior frontal cortex stimulation preceding right presupplementary motor area stimulation by either 4 ms (excitation condition) or 100 ms (control condition), and were subsequently administered the Stop Signal Task (SST) in both sessions.

Results. HCs showed decreased stop signal reaction time in the excitation condition ($t(19) = -3.01$, $p = 0.007$, [CIs]:−35.6 to −6.42); this facilitatory effect was not observed for AUD ($F(1,31) = 9.57$, $p = 0.004$, CIs: −68.64 to −14.11). Individually, rates of SST improvement were substantially higher for healthy (72%) relative to AUD (13.6%) groups (OR: 2.33, $p = 0.006$, CIs:−3.34 to −0.55).

Conclusion. In line with previous findings, cPAS improved response inhibition in healthy adults by strengthening the fronto-striatal network through putative long-term potentiation-like plasticity mechanisms. Furthermore, we identified a possible marker of impaired cortical excitability, and, thus, diminished capacity for cPAS-induced neuroplasticity in AUD with direct implications to a disorder-relevant cognitive process.

Introduction

The ability to effectively inhibit a craving is crucial to prevent relapse. Impairments in response inhibition – a form of impulsivity characterized by the inability to suppress suboptimal or inappropriate responses – are prevalent in neuropsychiatric disorders including addiction (Domínguez-Salas, Díaz-Batanero, Lozano-Rojas, & Verdejo-García, 2016; Verdejo-García, Lawrence, & Clark, 2008). Deficits in this domain can be assessed using experimental paradigms such as the Stop Signal Task (SST) (Logan, Zandt, Verbruggen, & Wagenmakers, 2014; Verbruggen & Logan, 2009) and Go/No-Go Task (Drewe, 1975; Garavan, Ross, & Stein, 1999), whereby individuals are required to withhold a prepotent motor action after the presentation of an external stopping cue (for a review, see Chambers, Garavan, & Bellgrove (2009)). In alcohol use disorder (AUD), impaired performance on these measures can be observed prior to alcohol use onset in at-risk individuals (Nigg et al., 2006; Squeglia, Jacobus, Nguyen-Louie, & Tapert, 2014), concurrently with chronic use (Lipszyc & Schachar, 2010), and in those prone to relapse within 1 year of treatment (Czapla et al., 2016; Rupp et al., 2016); suggesting that response inhibition contributes to multiple key alcohol-related outcomes (Groman, James, & Jentsch, 2009; Wilcox, Dekonenko, Mayer, Bogenschutz, & Turner, 2014).

Inhibitory control relies on the structural and functional integrity of the prefrontal cortex (PFC), which exerts 'top-down' influence via its abundant connections to a wide range of cortical and subcortical brain regions (Dalley, Everitt, & Robbins, 2011). Specific to

reactive stopping, rodent and human research has implicated fronto-striatal circuitry comprised of two PFC subregions – the right inferior frontal cortex (rIFC) and the dorsomedial frontal cortex (particularly, the presupplementary motor area [pre-SMA]) – which send hyperdirect projections to the subthalamic nucleus (STN) – a primary inhibitory hub of the basal ganglia (Aron, 2007, 2011). Information processing within this network begins with orientation toward the stopping cue by the PFC structures (Cai, Chen, Ide, Li, & Menon, 2017) which, in tandem, innervate the STN to suppress competing striatal output to the primary motor cortex (M1) – thus canceling the initiated action (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Jahfari et al., 2011).

Chronic alcohol use promotes a shift from PFC to striatal dominance over responding (Everitt & Robbins, 2005), leading to a loss of control over alcohol-seeking and consumption (Goldstein & Volkow, 2002). These large-scale alterations in PFC function and their behavioral sequelae in AUD are attributable, in part, to the impact of alcohol on both inhibitory (i.e. gamma-aminobutyric acid [GABA]-ergic) and excitatory (i.e. glutamatergic) synaptic transmission; the latter being a core regulator of experience-dependent neuroplasticity (Koob & Volkow, 2016). Extensive preclinical research in rodents indicates that acute alcohol administration produces an overall reduction in cortical excitability through the potentiation of selective GABA transmission and an accompanied suppression of glutamate release (Abrahao, Salinas, & Lovinger, 2017). Prolonged exposure, however, results in an enduring state of cortical hyperexcitability – via decreased GABAergic and increased glutamatergic output countering the inhibitory effect of acute consumption (Kalivas, 2009) – which facilitates the development and perseveration of alcohol dependence (Littleton, 2001).

In humans, transcranial magnetic stimulation (TMS) techniques have been applied to identify acute and chronic alcohol-related changes in intracortical inhibitory and excitatory processes *in vivo*. In line with neuromolecular evidence, healthy volunteers administered acute alcohol in single doses show enhanced inhibition in M1 (Conte et al., 2008; Ziemann, Lönnecker, & Paulus, 1995), and dampened excitability of the PFC (Kähkönen, Wilenius, Nikulin, Ollikainen, & Ilmoniemi, 2003); with a corresponding decrease in functional connectivity between these areas (Kähkönen et al., 2001). Conversely, clinical populations with AUD – including those with alcohol withdrawal syndrome (Nardone et al., 2010) – have shown reduced M1 (Conte et al., 2008; Quoilin, Wilhelm, Maurage, de Timary, & Duque, 2018) and PFC (Naim-Feil et al., 2016) inhibition, with more pronounced reductions linked to greater behavioral disinhibition at time of testing and likelihood of relapse at reassessment after 1 year (Quoilin et al., 2018). These observations are contrary to the global cortical hypoexcitability demonstrated in chronic nicotine (Lang, Hasan, Sueske, Paulus, & Nitsche, 2008) and cocaine (Boutros et al., 2001) use – likely due to the distinct receptor profiles of these drugs (Barr et al., 2011). Thus, translational findings indicate that chronic alcohol promotes a pathophysiology characterized by widespread neuroadaptations in both GABAergic (Hanlon, Dowdle, & Henderson, 2018; Quoilin et al., 2018; Zhou, Zhan, He, & Luo, 2019) and glutamatergic (Conte et al., 2008; Nardone, Trinka, Sebastianelli, Versace, & Saltuari, 2019) mediated systems implicated in cortical excitability, which may, in turn, adversely affect neuroplasticity reliant on these receptor activities (Aroniadou & Keller, 1995; Koob & Volkow, 2016).

Paired associative stimulation (PAS) is a TMS protocol by which the repeated delivery of low-frequency paired-pulses from two differing sources (e.g. cortical, median nerve, or deep brain stimulation) can modify excitability, and thus, functional activity between brain regions via spike-timing-dependent plasticity mechanisms (Stefan, Kunesch, Cohen, Benecke, & Classen, 2000). Cortical PAS (cPAS) involves the paired stimulation of two cortical sites, producing effects which seemingly extend to distant, yet interconnected subcortical regions which subserve more rudimentary behaviors (Burt, Lisanby, & Sackeim, 2002). In these protocols, the relative order of stimulation site and duration between (i.e. interstimulus interval [ISI]) paired-pulses can induce either excitation or inhibition; putatively reflecting long-term potentiation (LTP)-like or long-term depression (LTD)-like effects (Stefan et al., 2000). In line with the presumed involvement of plasticity mechanisms, the effects of PAS develop rapidly, endure beyond acute stimulation in a reversible manner (Stefan et al., 2000), and can be blocked by administration of drugs which interact with glutamate subtype N-methyl-D-aspartic (NMDA)-receptors (Wolters et al., 2003). Previous research aimed to induce short-term plasticity with PAS during acute alcohol administration in healthy volunteers has shown augmentation of LTD-like (Fuhl, Müller-Dahlhaus, Lücke, Toennes, & Ziemann, 2015) but disruption of LTP-like mechanisms in M1 (Loheswaran et al., 2016; Lücke et al., 2014) and the PFC (Loheswaran et al., 2017). These more standard PAS protocols used M1- or PFC-TMS preceded 25 milliseconds (ms) earlier by median nerve stimulation with either motor-evoked potential (MEP) or electroencephalograph (EEG) output as outcome measures. cPAS protocols also appear to affect MEP when the conditioning stimulus is applied to regions integrated with M1, such as contralateral M1 (Rizzo et al., 2009), supplementary motor area (Arai et al., 2011), and ventral premotor (Buch, Johnen, Nelissen, O'Shea, & Rushworth, 2011) and posterior parietal (Veniero, Ponzo, & Koch, 2013) cortices. However, cPAS has not been used in individuals with chronic exposure to alcohol.

Recently, our research group demonstrated that a novel cPAS protocol targeting the rIFC and pre-SMA putatively influencing the STN hyperdirect pathway improved response inhibition – particularly for older (⩾30 years) adults – in two separate healthy samples. Specifically, when rIFC was stimulated 4 ms prior to pre-SMA, it was presumed this repeated pairing concomitantly strengthened pre-SMA to STN input; consequently facilitating faster reactive stopping (Kohl et al., 2018; Mandali, Tsurumi, Popa, & Voon, 2021). (For further discussion of the logic behind our cPAS protocol, see Kohl et al. (2018).) Importantly, cPAS delivered to this circuit influenced response inhibition with no effect on delay discounting – a dissociable form of impulsivity wherein choice preference for small, immediate rewards outweighs that for delayed, yet larger rewards (Voon & Dalley, 2016) – thus indicating target specificity of the cPAS intervention (Kohl et al., 2018). To our knowledge, no prior research has examined whether cPAS can modulate this disorder-relevant cognitive process as a function of chronic alcohol use. Thus, in the current study, we assessed plasticity of the inhibitory network in AUD *v.* healthy controls (HC) with a cPAS protocol targeting the rIFC and pre-SMA, and measured response inhibition using the SST.

Materials and methods

Participants

We contacted 55 potential participants from the greater Cambridgeshire area, United Kingdom (UK). Twenty patients

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meeting the criteria for the Diagnostic and Statistical Manual of Mental Disorders Fifth-Edition (DSM-V-TR; American Psychiatric Association, 2013) AUD (26–74 years, 6 [30%] females) were recruited from the outpatient hepatology clinic at the University of Cambridge Addenbrooke's medical site, with a majority diagnosed with moderate to severe alcohol-related liver disease (ARLD) at time of testing (patient somatic health status is reported in online Supplemental Material Section 1); of these patients, 15 reported they were fully abstinent from alcohol, while five reported their condition as ongoing. Thirty-five HCs (23–73 years, 11 [31.4%] females) were enrolled via SONA online research recruitment system; within the sample of 35 HCs, 20 (26–73 years, 6 [30%] females) were matched for age, gender, and years of education with AUD patients.

Safety screening for all participants undergoing TMS was undertaken via either phone or in-person interview by a trained research assistant. Exclusion criteria included TMS contraindications, past or current major neurological or psychiatric disorders, and undergoing pharmacotherapy programs that could influence task performance or neurological activity (including benzodiazepine or withdrawal medications). Further exclusion criteria for HCs included any past or current Substance Use Disorder (SUD), while AUD patients were excluded if they reported co-morbid SUDs or chronic polysubstance (with the exception of nicotine) use. All participants reported a right-handed predominance.

Upon arrival at the testing center, participants were briefed about the experimental design and gave written informed consent, and were reimbursed £7.50 per hour for study participation. All experimental procedures contributing to this work were approved by the University of Cambridge Research Ethics Committee and performed according to the ethical standards of the Declaration of Helsinki, as revised in 2008.

Response inhibition measure

Response inhibition was assessed with the SST (Cambridge Cognition, Cambridge, UK; Figure 1A); all task audio and visual stimuli were produced by and participant responses recorded on a portable computer monitor. Participants were instructed to respond as quickly as possible to an arrow pointing in either a right or left direction (go signal) by pressing one of two buttons on a button box connected to the monitor with the right or left index finger coinciding with the direction of the arrow. If an audio tone (stop signal) was presented, the participants were required to withhold the response. The stop signal onset time was step-wise modified by the stopping success of the previous response.

SST performance can be influenced by factors related to execution of the motor response including signal discrimination (measured in amount of direction errors), reaction time (measured as the mean reaction time on go trials), and stopping accuracy (measured by the proportion of successful stops during stop trials), as well as interacting control mechanisms involved in performance monitoring and adjustment (for a review, see Verbruggen & Logan, 2008). Taken together, the primary outcome measure of interest is stop signal reaction time (SSRT); defined as the median reaction time on trials correctly performed with a button press response subtracted from the stop signal delay (Logan et al., 2014). The lower the SSRT – or the less time necessary to cancel a motor response prompted by the stopping cue – the greater capacity for response inhibition.

Self-report measures

A series of self-report psychiatric measures were employed at baseline. The Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993) and the Fagerström Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991) assessed the severity of alcohol and nicotine use, respectively. Current clinical status was assessed using Beck's Depression Inventory (BDI-II; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and the State-Trait Anxiety Inventory (STAI; Julian, 2011). Two forms of impulsivity separable from response inhibition were assessed with: (1) the Impulsive-Behaviors Scale (UPPS-P; Whiteside & Lynam, 2001) which contains five trait impulsivity subscales: lack of perseveration, lack of premeditation, sensation-

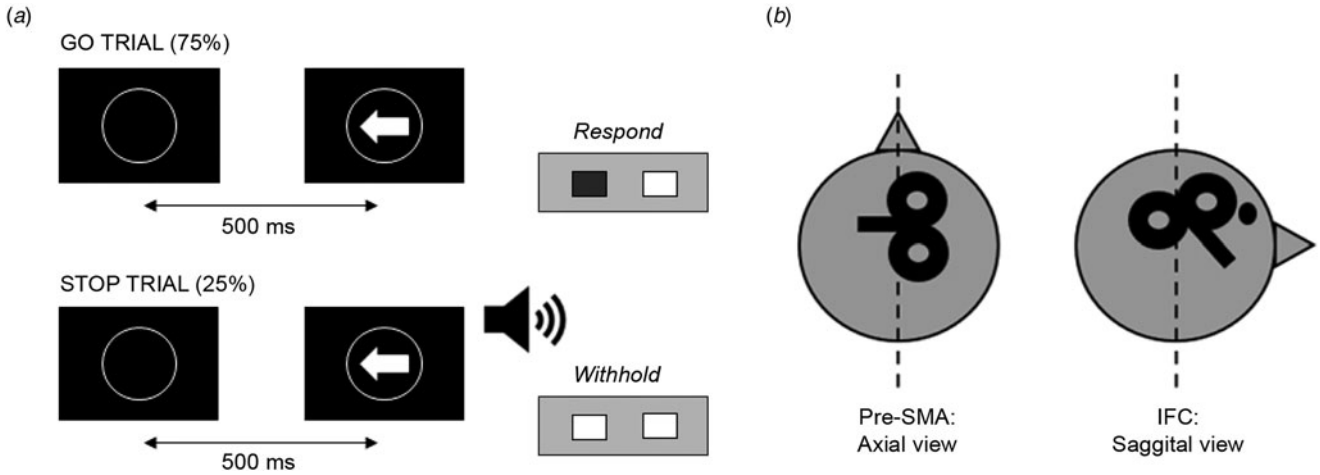

Figure 1. Response inhibition measure and cortical paired associative stimulation (cPAS) coil location target and orientation. (**A**) Stop Signal Task (SST) schematic. (**B**) Stimulation coil location and orientation. Coil 1 was placed over the right IFC (MNI coordinates [in mm]: x = 48, y = 16, z = 16) at a 20° angle to the coronal plane (shown here in a sagittal view), while coil 2 was placed over the right pre-SMA (MNI coordinates [in mm]: x = 10, y = 10, z = 60) parallel to the midline (shown here in an axial view).

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seeking, negative urgency, and positive urgency; and (2) the Monetary Choice Questionnaire (MCQ; Kirby, Petry, & Bickel, 1999) which measures delay discounting; the more quickly the reward loses value as a function of delay (represented by an increase in K value), the more impulsive the individual is considered.

Stimulation protocol

We delivered two off-line cPAS protocols. In both protocols, we first used neuronavigation for precise targeting registered to Montreal Neurological Institute (MNI) space (Brainsight; Rogue Research Inc., Montreal, Quebec, Canada). Resting motor threshold (RMT) was assessed via single TMS pulses to right M1, defined as the lowest intensity stimulation to effectively elicit responses from the first dorsal interosseous muscle of the participant's non-dominant hand (i.e. MEPs) as monitored by electromyograph (EMG) acquired through Signal software (Cambridge Electronics design, Cambridge, UK).

For cPAS, stimulation pulses were administered using two Magstim 2002 machines (Magstim Company Limited, Whitland, UK) via two 70-mm figure-of-eight air-film coils. Coil targets in the form of MNI coordinates were derived from a functional imaging meta-analysis of response inhibition (Cieslik, Mueller, Eickhoff, Langner, & Eickhoff, 2015). Coil 1 was situated over the rIFC (MNI target site [in mm]: x = 48, y = 16, z = 16) at a 20° angle to the coronal plane, and coil 2 was situated over the right pre-SMA (MNI target site [in mm]: x = 10, y = 10, z = 60) parallel to the midline when viewed axially (Fig. 1B). Pulse intensity was set to 120% of RMT. Both cPAS sessions comprised 100 pairs of stimuli at 0.2 Hz to achieve an 8.3-minute duration.

The two cPAS conditions varied in the ISI of the paired pulses: (1) rIFC stimulation preceded right pre-SMA stimulation by 4 ms (i.e. IFC + 4), and (2) rIFC stimulation preceded right pre-SMA stimulation by 100 ms (i.e. IFC + 100). The former served as the experimental condition based on evidence of modulatory effects on the cortico-subcortical response inhibition network in our previous studies (Kohl et al., 2018; Mandali et al., 2021). The latter served as a control condition, as the duration between paired pulses is presumed to be too protracted a period to facilitate either cortico-cortical (Buch et al., 2011) or cortico-subcortical conduction (Lu, Tsai, & Ziemann, 2012).

Experimental design

We used a single-blind between-subjects design to investigate the effects of cPAS targeting the response inhibition network in AUD and HC adults, consisting of two cPAS sessions delivered in randomized order at least 7-days apart (Fig. 2A). Prior to the cPAS intervention of the first session, participants completed the baseline self-report measures. Post-cPAS in both sessions, participants undertook the SST within the half-an-hour duration by which the cPAS intervention is purportedly active (Stefan et al., 2000).

Statistical analysis

Statistical analyses were conducted in JASP (Version 0.16.0). First, all data were assessed for normality (Shapiro-Wilk test $p > 0.05$), homogeneity of variance (Levene's test $p > 0.05$), and outliers (>3 standard deviations from the group mean) to employ the appropriate t test for the variable type(s) according to statistical assumptions met.

Our primary variable of interest was mean SSRT (in milliseconds). Differences in within-group SSRT were assessed using paired samples t tests. Between-group differences were assessed by removing the variance of the control SSRT (IFC + 100) from experimental SSRT (IFC + 4) to perform independent samples t tests. We then used a one-way ANCOVA model to confirm between-group differences while controlling for variables informed by self-report measures. Concurrent nicotine use was also controlled for in this model given its observed effects on PAS LTP-like plasticity induction (Grundey et al., 2012; Thirugnanasambandam et al., 2011). Next, we examined the proportion of those who improved SSRT in the IFC + 4 condition compared between groups using a stepwise logistic regression to compute odds ratio. Finally, Spearman correlations were performed to assess whether SST performance was related to independent measures of impulsivity (i.e. UPPS-P and MCQ).

We observed 20 participants per group was sufficient to demonstrate, under standard assumptions (80% power, alpha-level = 0.05), effect sizes of greater than or equal to 0.22 (partial eta squared) and 0.8 (Cohen's d) across significant results. Furthermore, our sample size was consistent with or exceeded the sample sizes of previous TMS studies in plasticity induction in alcohol use (Fuhl et al., 2015; Loheswaran et al., 2016; 2017; Lücke et al., 2014). All tests were two-tailed with significance assigned at $p < 0.05$, and Bonferroni corrected for multiple comparisons. Confidence intervals are provided for all statistically significant findings.

Results

Demographic and psychiatric factors

The matched HC group showed lower alcohol use frequency and severity as well as lesser severity of psychiatric factors depression, anxiety, and urgency impulsivity than the AUD group. The AUD group also more quickly discounted delayed rewards. Demographic and psychiatric characteristics for the AUD and matched HC ($N = 20$) groups are summarized in Table 1. Compared to the larger HC group ($N = 35$), the AUD group was significantly older and had undergone less years of formal education, while showing similar differences in psychiatric factors observed with the matched HCs. Full demographic and psychiatric characteristics for the larger HC group are summarized in online Supplemental Material Section 2.

RMT in AUD and HC groups

The average RMT of the AUD (IFC + 4: 44.5 ± 6.65, IFC + 100: 45.2 ± 7.12) group did not significantly differ from matched HC (IFC + 4: 42 ± 6.74, IFC + 100: 42.5 ± 5.41) group ($p > 0.05$).

SST practice effects and cPAS plasticity induction carryover

SST practice effects were indexed by comparing mean SSRT as a function of testing session order. Participants who underwent IFC + 4 cPAS during their first testing session ($N = 27$; 174 ± 64.4) did not significantly differ in mean IFC + 4 SSRT than those who underwent IFC + 4 cPAS during their second testing session ($N = 28$; 158.5 ± 45.4) ($p > 0.05$). Additionally, no significant differences were observed in mean IFC + 100 SSRT between those who underwent IFC + 4 cPAS during their first (157.2 ± 34.7) *v.* their second (186.3 ± 65.3) testing session ($p > 0.05$),

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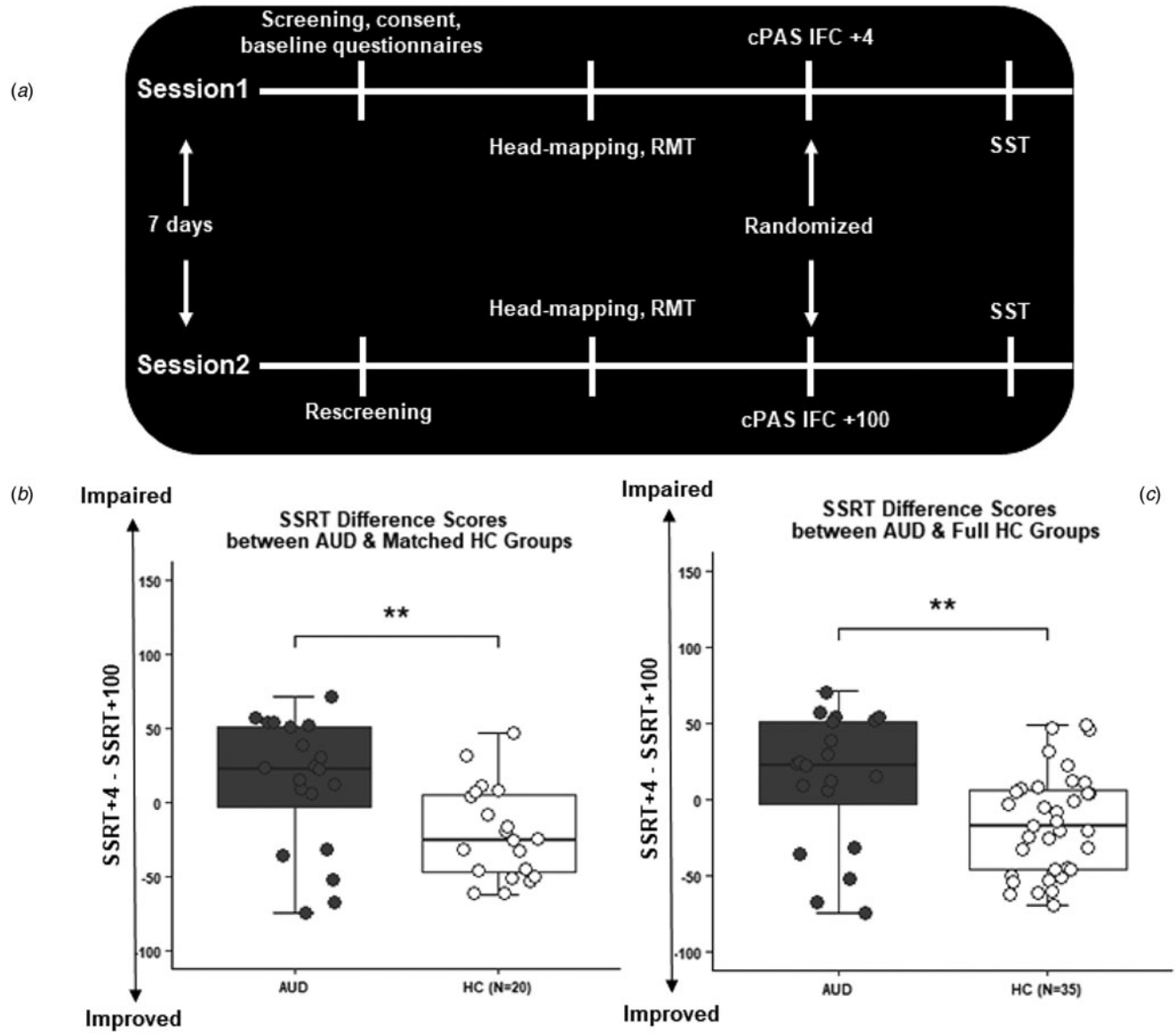

Figure 2. Experimental design and results from cortical paired associative stimulation (cPAS) intervention on Stop Signal Task (SST) performance. (**A**) Experimental design. (**B**) Boxplot of mean difference of SST performance during the control (IFC + 100) condition and experimental (IFC + 4) condition in alcohol use disorder (AUD) and matched ($N = 20$) healthy control (HC) groups. The matched HC group, but not the AUD group, significantly improved SST performance in the experimental condition controlling for the variance of the control condition. (**C**) Boxplot of mean difference of SST performance during the control (IFC + 100) condition and experimental (IFC + 4) condition in alcohol use disorder (AUD) and larger ($N = 35$) healthy control (HC) groups. Performance of the larger HC group adhered to that of the matched HC group. $p < 0.05$*, $p < 0.01$**. Error bars denote standard error.

further indicating adequate wash out of the plasticity enhancing effects of IFC + 4 cPAS on SST performance in the control condition.

cPAS effects on SST performance in AUD and healthy controls

The matched HC group ($N = 20$) showed faster average SSRT in the IFC + 4 condition (152.2 ± 58.4) compared to the IFC + 100 condition (173.2 ± 48.4), t(19) = −3.01, $p = 0.007$, CIs:−35.6 to −6.42. Conversely, in the AUD group, there was no significant difference in SST performance between IFC + 4 (184.4 ± 61.7) and IFC + 100 (169.9 ± 64.2) conditions ($p > 0.05$). Notably, the HC and AUD groups did not differ in control SSRT as assessed by the IFC + 100 condition ($p > 0.05$). However, the HC group (−21 ± 31.2) as compared to the AUD group (14.5 ± 54.7) showed a significant facilitation in SST performance in the IFC + 4 condition, t(38) = −2.52, $p = 0.02$, CIs: −64.01 to −7; Figure 2B).

Within- and between-group SST performance of the larger HC group ($N = 35$) adhered to that of the matched HCs (Fig. 2C; data found in online Supplementary Materials Section 3), while the abstinent AUD ($N = 15$) performance adhered to that of the full AUD ($N = 20$) group (online Supplementary Materials Section 4.1).

ANCOVA model of SST performance controlling for psychiatric factors

We used a one-way ANCOVA model with mean SSRT difference score as our dependent variable and group (i.e. AUD [$N = 20$] *v.*

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Table 1. Demographic and psychiatric factors between alcohol use disorder (AUD) and gender- and age-matched ($N = 20$) healthy control (HC) groups

Factor		AUD mean(s.d.)	HC mean(s.d.)	Test	Statistic	Df	*p*-Value	CIs
Age		52.5(12.8)	47.5(13.1)	Mann–Whitney	151.5	N/A	0.19	
Gender		0.3(0.47)	0.3(0.47)	Mann–Whitney	200.0	N/A	0.99	
Years of education		15(3.28)	16(2.45)	Student	−1.25	1,38	0.29	
Alcohol use		15(10.54)	5(4.9)	Welch	−3.85	1,26.8	<0.001**	−15.3 to −4.7
Nicotine use		1(1.8)	0.5(1.23)	Mann–Whitney	169	N/A	0.26	
Depression		11.4(9.5)	5.9(6.9)	Welch	−2.1	1,34.7	0.04*	−10.8 to −0.2
Anxiety		22.18(8.2)	16.6(5.89)	Welch	−2.46	1,34.5	0.02*	−10.1 to −1
Trait Impulsivity	SS	28.4(7.9)	25.8(10.2)	Mann–Whitney	204	N/A	0.92	
	NU	28.4(7.72)	21.2(8)	Mann–Whitney	106	N/A	0.01*	−11 to −2
	PU	27.6(6.78)	22(6.7)	Mann–Whitney	122	N/A	0.04*	−9.9 to −1.3
	LOPre	22.2(5.04)	19.4(7.82)	Mann–Whitney	174	N/A	0.49	
	LOPer	21.3(5.58)	17.8(7.1)	Mann–Whitney	150	N/A	0.18	
Delay discounting (*K*)		0.03(0.04)	0.007(0.01)	Welch	3.75	1,36.3	<0.001**	0.004–0.04

Factor = type of demographic or psychiatric factor under evaluation (from top to bottom: age, gender [in proportion of females], years of education, alcohol use [AUDIT], nicotine use [Fagerström], depression [BDI-II], anxiety [STAI], impulsivity [UPPS-P] with subscales sensation-seeking [SS], negative urgency [NU], positive urgency [PU], lack of premeditation [LOPre], and lack of perseveration [LOPer], and delay discounting [MCQ, *K* value]); AUD mean (s.d.) = the mean and standard deviation in the AUD group by factor; HC mean (s.d.) = the mean and standard deviation in the HC group by factor; Test = type of *t* test used according to statistical assumptions met; Statistic = test statistic; Df = degrees of freedom; *p*-Value = significance level of test (asterisks by a *p*-value indicate statistical significance; $p < 0.05$*, $p < 0.005$**); CIs = confidence intervals of average (i.e. mean or median) group difference for each statistically significant finding

HC [$N = 20$]) and testing session order (i.e. IFC + 4 first [$N = 20$] *v.* IFC + 4 s [$N = 20$]) as fixed factors, controlling for nicotine use severity, depression, anxiety, and negative and positive urgency impulsivity as covariates of no interest. No covariate was correlated to another greater than rho = .67. We showed a significant main effect of group ($F(1,31) = 9.57$, $p = 0.004$, CIs: −68.64 to −14.11), with an insignificant group*testing order interaction and no covariates related to SSRT difference score ($p > 0.05$). These results were confirmed in two separate ANCOVAs, using: (1) the abstinent AUD group ($N = 15$) with the same covariates ($F(1,26) = 7.67$, $p = 0.01$, CIs: −94.64 to −13.99), and (2) the larger HC group ($N = 35$) controlling also for age and years of education ($F(1,44) = 11.84$, $p = 0.001$, CIs: 18.64–71.37).

Logistic regression of SSRT improvement in IFC + 4 cPAS

Fourteen of 20 (70%) HC compared to 5 of 20 (25%) AUD improved SST performance in the experimental condition. A stepwise logistic regression model using observed SSRT performance improvement in the IFC + 4 condition (i.e. yes = 1/no = 0) as a dependent variable and group as a fixed factor was statistically significant (X^2 [38, $N = 40$] = 8.42, $p = 0.004$); this model explained 25.3% (Nagelkerke R^2) of the variance in SSRT improvement between-groups and correctly classified 72.5% of cases. Overall, HC group designation was associated with more than twice higher likelihood of SSRT improvement in the IFC + 4 cPAS condition (HCs: 72% *v.* AUD: 13.6%; odds ratio: 2.33; $p = 0.006$; CIs: −3.34 to −0.55, Fig. 3). A separate stepwise logistic regression analysis performed using the abstinent AUD group ($N = 15$) produced comparable results (model summary found in online Supplemental Materials Section 4.2).

SST performance relationships to impulsivity measures

SSRT in the IFC + 4 and IFC + 100 conditions, as well as the SSRT difference score between these conditions, were unrelated to any UPPS-P subscale or MCQ scores (all − 0.12 < rho <0.24 and $p > 0.22$).

Discussion

Deficits in inhibitory control are commonly observed in addiction disorders (Domínguez-Salas et al., 2016; Verdejo-García et al., 2008), with impaired performance in Go/No-Go and SST (Chambers et al., 2009). Under these paradigms, convergent multimodal evidence has implicated fronto-striatal circuitry, including two PFC subregions – the rIFC and pre-SMA – which extend to the STN; this 'hyperdirect' network is believed to be essential for the successful application of fast, reactive stopping behaviors (Aron, 2007, 2011). The specific contributions of these areas to inhibitory control have been theorized; it is suggested that the rIFC is crucial for salience detection of the stopping cue (Cai et al., 2017), and the pre-SMA for action monitoring (Bonini et al., 2014), with rIFC expediting the stop signal prior to the pre-SMA (Duann, Ide, Luo, & Li, 2009). The STN – which integrates this critical input from the PFC (Aron,

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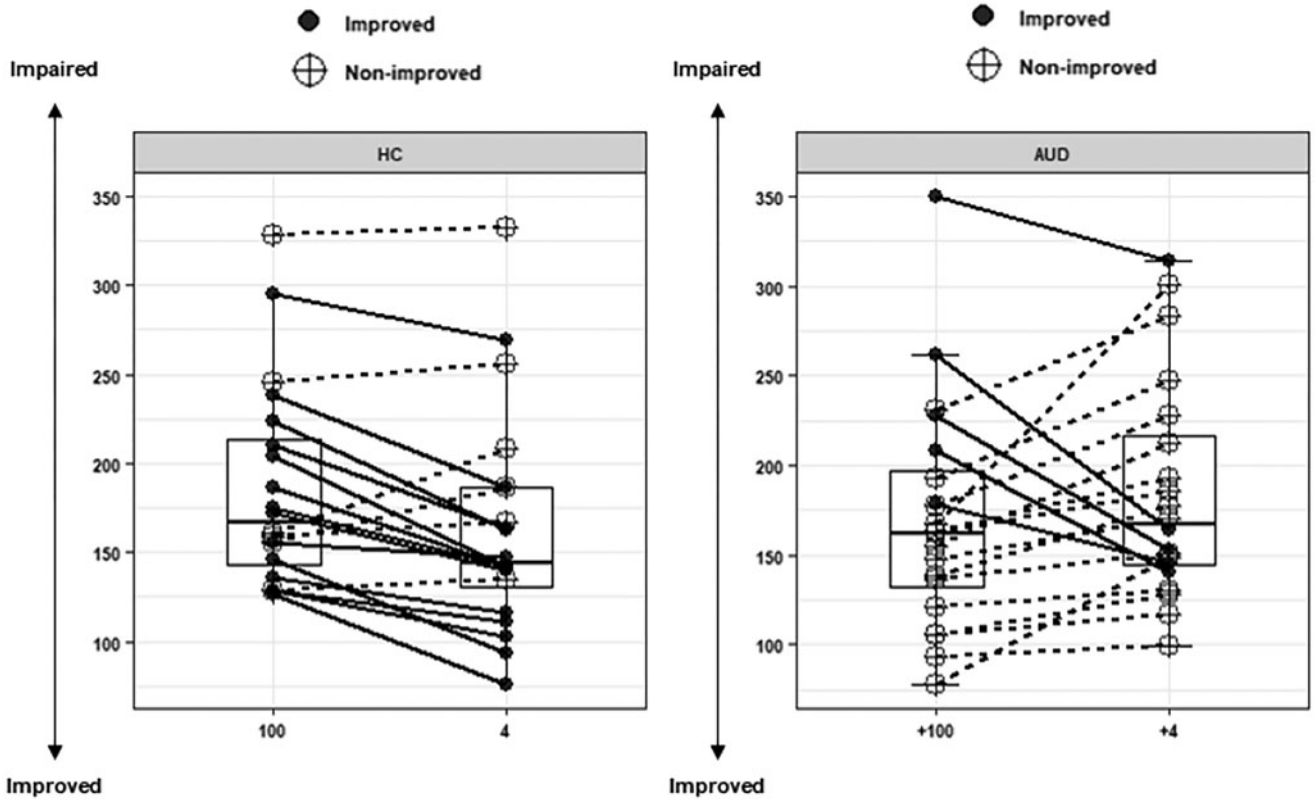

Figure 3. Proportion of those improved in stop signal reaction time (SSRT) in healthy control (HC- left) and alcohol use disorder (AUD- right) groups after cortical paired associative stimulation (cPAS) intervention. Solid black lines traced from solid black dots indicate an improvement (and the slope indicates the extent of the improvement) in SSRT in the IFC + 4 cPAS condition, while dotted black lines traced from open dots indicate an impairment (and the slope indicates the extent of the impairment) in SSRT in the IFC + 4 cPAS condition. HC group designation was associated with significant improvement in SSRT in the IFC + 4 cPAS condition, with a majority of HCs showing this effect.

2007; Obeso et al., 2017) – then performs response selection to cancel the prepotent action (Bastin et al., 2014; Kühn et al., 2008).

Here, we used cPAS – a repetitive paired-pulse TMS protocol purported to induce cortical synaptic plasticity (Stefan et al., 2000) – to strengthen the efficiency of this inhibitory network in AUD and HC adults, and compared group differences in responsivity on the SST. We showed that, post-cPAS, HC adults demonstrated an overall decrease in SSRT – the key measure of inhibitory control (Logan et al., 2014) – thereby replicating findings of two studies from our research group (Kohl et al., 2018; Mandali et al., 2021). It was posited that rIFC stimulation delivered 4 ms prior to pre-SMA stimulation had primed the pre-SMA to STN connection critical to reactive stopping (Obeso et al., 2017), thereby improving response inhibition (Kohl et al., 2018). Importantly, inhibitory control facilitated by this protocol in our prior studies appeared to be specific to older (⩾30 years) adults, in line with findings that pre-SMA to STN anatomical connectivity strength more robustly predicts SST performance as age increases (Coxon, Impe, Wenderoth, & Swinnen, 2012).

Conversely, AUD adults matched for age failed to show similar levels of improvement in SST performance after the same cPAS intervention, with a small minority of AUD showing decreased SSRT post-cPAS. These results may reflect the progressively detrimental effects of chronic alcohol use on PFC circuitry (for a review, see Moselhy, Georgiou, & Kahn (2001)). In AUD, diminished recruitment of the PFC has been observed in a range of executive functioning tasks (Mann, Günther, Stetter, & Ackermann, 1999), with weaker functional connectivity between the PFC and striatum shown during SST performance (Courtney, Ghahremani, & Ray, 2013). AUD adults also present regional atrophy (Cardenas et al., 2011; Chanraud et al., 2007; Makris et al., 2008), as well as abnormalities in frontal lobular blood flow (Noël et al., 2002), associated with the development and perseveration of alcohol-seeking behaviors (Goldstein & Volkow, 2002), and probability of relapse (Noël et al., 2002).

Alcohol-related PFC changes at the macroscopic level may be ascribed to the effects of alcohol on the efficacy of synaptic transmission and function (Koob & Volkow, 2016). In rodent models, acute administration promotes inhibitory processes (Abrahao et al., 2017), while chronic use leads to a compensatory increase in global cortical excitability via a reduction of GABAergic and concomitant upregulation of glutamatergic transmission and NMDA-receptor release (Kalivas, 2009). Studies in humans applying TMS to index these mechanisms of altered regional cortical excitability during acute (Conte et al., 2008; Kähkönen et al., 2001, 2003; Ziemann et al., 1995) and after recurrent (Conte et al., 2008; Naim-Feil et al., 2016; Nardone et al., 2010; Quoilin et al., 2018) use have provided support for this neuromolecular data. Thus, even during prolonged periods of abstinence (i.e. post-withdrawal), it appears these widespread neuroadaptations in cortical excitability persist in an allostatic manner (Koob, 2009), which may result in enduring changes to experience-dependent synaptic plasticity processes including LTP and LTD (Koob & Volkow, 2016).

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The well-documented effects of repeated alcohol exposure on glutamatergic transmission (particularly its actions on NMDA-receptors) in the PFC, and its role in synaptic functioning (Kalivas, 2009), may provide insight into the current findings. For instance, pathologically high levels of extracellular glutamate may result in excitotoxic changes in morphology such as aberrant synaptic pruning (Ferrer, Galofro, Fobregues, & Lopez-Tejero, 1989), myelin reduction (Pfefferbaum & Sullivan, 2005), and selective cellular loss (Chandler, Sutton, Norwood, Sumners, & Crews, 1997) within PFC circuits; all factors which contribute to the efficacy of neuronal communication. Likewise, it is plausible – given that NMDA receptor activation interferes with LTP (Huang, Colino, Selig, & Malenka, 1992), and that acute alcohol administration reduces short-term LTP-like plasticity in the human cortex (Loheswaran et al., 2016; 2017; Lücke et al., 2014) – that a continued state of glutamatergic upregulation may have rendered those with AUD less receptive to stimulation interventions aimed at plasticity induction relative to their HC counterparts (Chiamulera, Piva, & Abraham, 2021). Our findings, then, suggest that pre-existing alcohol-related neuroadaptations on the neurotransmitter level (especially that of glutamatergic dysregulation) may have weakened the capacity for cPAS to enhance inhibitory control – a cognitive process highly relevant to the trajectory of AUD (Groman et al., 2009; Wilcox et al., 2014).

The AUD group demonstrated higher levels of trait impulsivity compared to HCs as measured by the UPPS-P; these elevations were specific to the positive and negative urgency subscales, which assess the tendency to act rashly in an intensified euphoric or aversive emotional state, respectively (Cyders & Smith, 2007). AUD also showed steeper delay discounting on the MCQ. Both decisional impulsivity and mood-based impulsive personality traits are strongly associated with addiction disorders (Amlung, Vedelago, Acker, Balodis, & MacKillop, 2017; Zorrilla & Koob, 2019), yet map onto distinct neural circuitry from that involved in response inhibition (Voon & Dalley, 2016). Thus, that UPPS-P and MCQ scores were unrelated to SST performance in both control and excitation conditions for either group underscores the dissociability of impulsivity subtypes (MacKillop et al., 2016), as well as the target specificity of our cPAS intervention (Kohl et al., 2018).

Trait and decisional impulsivity are relatively stable characteristics, while motor disinhibition can fluctuate naturally and improve with cognitive training (Houben, Nederkoorn, Wiers, & Jansen, 2011; Jones, Christiansen, Nederkoorn, Houben, & Field, 2013). Furthermore, neuroadaptive changes at glutamatergic synapses which appear to diminish responsivity to plasticity induction can potentially be counteracted with pharmacological agents (Chiamulera et al., 2021), such as NMDA channel blocker, ketamine (Fattore, Piva, Zanda, Fumagalli, & Chiamulera, 2018). Such agents – which are purported to amplify the malleability of neuronal circuits (Chiamulera et al., 2021)– have been combined with TMS protocols to treat symptoms of neuropsychiatric disorders in intractable states (Best, Pavel, & Haustrup, 2019; Pradhan, Parikh, Makani, & Sahoo, 2015). Preliminary evidence indicates that improved response inhibition attenuates alcohol cue-induced craving (Papachristou et al., 2013) and intake (Houben et al., 2011); thus, future research is required to delineate the role of noninvasive neuromodulation – possibly paired with pharmacological agents which may increase responsivity to intervention (Fattore et al., 2018)– to enhance fronto-striatal integrity underlying inhibitory control and, in turn, mitigate adverse alcohol-related outcomes in AUD.

Limitations and future directions

This study was not without limitations which future research can overcome. First, we obtained a convenience sample of AUD patients from the hepatology clinic with varying stages of sobriety as well as self-reported polysubstance non-use. A subsample analysis confirms that our findings apply to abstinent AUD without the confounding effect of ongoing alcohol consumption. However, as duration of abstinence is related to executive functioning recovery (Kopera et al., 2012; Moselhy et al., 2001), and under-reporting biases associated with self-reported illicit drug use (Macleod, Hickman, & Smith, 2005), larger-scale neuromodulation studies in AUD may include a detailed abstinence timeline screening procedure in addition to a physiological index of alcohol (e.g. phosphatidylethanol) and illicit drug use status for both patient and HC groups as a means of participant exclusion, *post hoc* statistical covariance, or subgrouping (e.g. short- *v.* long-term abstinence) to interrogate factors linked to interindividual variation in responsivity to intervention.

Next, the proportion of males in our AUD sample was greater than females; reflective of the well-established trend of males more likely engaging in problematic alcohol use behaviors (Slade et al., 2016). Given further evidence of gender-specific differences in cortical reactivity to alcohol administration (Hoppenbrouwers, Hofman, & Schutter, 2010), the results of our cPAS intervention are perhaps more representative of the variation within the AUD population than would be expected from a gender-balanced sample. However, recent longitudinal meta-analyses have demonstrated a marked decrease in the male-female alcohol use gap (Slade et al., 2016). Thus, gendered cohort studies comparing differential capacity for plasticity induction in chronic alcohol are indicated.

Further, depressive and anxious symptoms were more pronounced in AUD compared to HC groups – a psychiatric phenomenon commonly observed in AUD populations (Lai, Cleary, Sitharthan, & Hunt, 2015). To address this discrepancy, we excluded participants who met the criteria for clinical depression ($\geqslant$23) or anxiety (>39); this ensured mean BDI-II and STAI scores in our AUD sample were well within the non-pathological range (Beck et al., 1961; Julian, 2011). Additionally, all ANCOVA models included BDI-II and STAI scores as covariates, showing neither main nor interactive effects of these potential confounds on SST performance between groups.

Finally, we postulated that the efficacy of cPAS in improving response inhibition is derived from a priming effect of rIFC stimulation on plasticity at the pre-SMA to STN connection. However, the precise mechanisms underlying cPAS, which appear to modulate relationships among these substrates within the inhibitory network, remain to be delineated. Our study did not incorporate physiological TMS measures of intracortical excitation and inhibition or contemporaneous functional imaging, which may provide insight into the processes contributing to differential changes in SST performance. Thus, further studies are required to confirm our preliminary behavioral findings and may integrate TMS or functional imaging paradigms to extend findings mechanistically.

Conclusion

We used cPAS to modulate the rIFC and pre-SMA to STN hyperdirect pathway and modify SST performance in AUD. Our results are two-fold. First, conferring further validity to our novel

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stimulation method, we replicate previous findings that cPAS targeting the inhibitory network decreases SSRT in healthy adults – presumably by priming the pre-SMA to STN function crucial to the successful execution of stopping behaviors. Second, AUD patients failed to show SST improvement with the same intervention; this may reflect altered cortical excitability resulting from widespread neuroadaptations associated with problematic forms of alcohol use. Thus, we identify a potential marker of impairment with direct implications to a disorder-relevant cognitive process underlying AUD. Further research is required to confirm our preliminary findings, as well as expand the role of noninvasive neuromodulation – potentially paired with pharmacological agents for increased intervention responsivity – in strengthening fronto-striatal networks implicated in inhibitory control in addicted populations.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723002374.

Data availability. Deidentified participant data is available on reasonable request from the corresponding author.

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Competing interest. None.

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