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Augmented tendency to act and altered impulse control in alcohol use disorders

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ABSTRACT

Action preparation relies on the operation of control processes that modulate the excitability of the corticospinal tract. On the one hand, excitatory processes prepare the motor system for the forthcoming response; the stronger these influences, the stronger the tendency to act. On the other hand, inhibitory influences allow to suppress inappropriate actions and, more generally, to ensure some sort of impulse control. Because an impairment in these processes could foster inappropriate drinking behavior, the present study aimed at evaluating the motor correlates of such excitatory and inhibitory influences in non-treatment seeking heavy drinkers (HDs) and in-patients suffering from severe alcohol use disorder (SAUDs). Besides, as cue-elicited craving might further alter these processes, we also assessed the impact of an alcohol-related exposure. To do so, 15 healthy controls (HCs), 15 HDs and 15 SAUDs performed a choice reaction time task after having been immersed in a neutral or an alcohol-related environment, using virtual reality videos. Importantly, single-pulse transcranial magnetic stimulation was applied over the left and the right primary motor cortex during the task to elicit motor-evoked potentials in a set of hand muscles allowing us to specifically probe the impact of excitatory and inhibitory processes on motor activity. Our data indicate that excitatory influences are particularly high in both HDs and SAUDs, especially in the dominant hand, an effect that was not observed in HCs. By contrast, inhibitory influences were found to be perfectly normal in HDs, while they were lacking in SAUDs. Furthermore, the alcohol-related exposure enhanced the level of self-reported craving, but this effect only arose in HDs and did not significantly alter the strength of excitatory and inhibitory influences. Overall, although these results have to be taken with caution due to the small sample sizes, this study suggests that enhanced excitatory processes characterize both HDs and SAUDs, while weaker inhibitory influences only concern SAUDs. Hence, an abnormally strong tendency to act could represent a common feature of hazardous drinking, leading individuals to excessive alcohol consumption, whereas deficient impulse control would be a hallmark of more severe forms of AUD, potentially due to the chronic neurotoxic effects of alcohol. Finally, although an alcohol-related exposure does not seem to affect excitatory and inhibitory processes at play during action preparation *per se*, future works should evaluate changes in corticospinal excitability during the preparation of responses specifically targeting alcohol-related cues.

1. Introduction

Alcohol craving, defined as the strong urge or irrepressible desire to drink alcohol, is a key element of alcohol use disorder (AUD), now listed as a crucial diagnostic criterion in the DSM-5 (American Psychiatric Association, 2013; van Lier et al., 2018). This phenomenon has been related to the risk of relapse in abstinent patients suffering from severe AUD (SAUDs) (Stohs et al., 2019; Weinland et al., 2019) and to addiction severity (Witteman et al., 2015). Furthermore, craving predicts subsequent alcohol use in individuals who are not seeking for treatment and do not have a diagnosis of AUD but are heavy drinkers (HDs) (Field and Jones, 2017; Jones et al., 2013).

Cue reactivity studies have largely demonstrated that one of the main factors triggering alcohol craving is the confrontation to alcohol-related stimuli. As such, the level of craving reported by HDs and SAUDs increases after an exposure to olfactory or visual alcohol-related cues (Field and Jones, 2017; Kreusch et al., 2017; Mainz et al., 2012) or a virtual immersion in an alcohol-related environment (Bordnick et al.,

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2008; Simon et al., 2020). This cue reactivity has been explained by classical conditioning theories: stimuli regularly associated with alcohol consumption would acquire incentive motivational properties, causing those cues to capture attention and to activate automatic approach behaviors (Robinson and Berridge, 1993; Wiers et al., 2007). Inhibitory control would be then required to overcome these conditioned urges to drink. Yet, patients suffering from SAUDs display a lack of inhibitory control, a deficit that is also reported in HDs and perceived as a risk factor for developing AUD (Dick et al., 2010; Smith et al., 2014). Moreover, some lines of evidence suggest that inhibitory abilities of SAUDs and HDs further drop during exposure to alcohol-related cues (Field and Jones, 2017; Gauggel et al., 2010), although this effect is still debated (Jones et al., 2013; Kreusch et al., 2017; Mainz et al., 2012). Overall, this literature indicates that when SAUDs and HDs are exposed to an alcohol-related environment, they experience a strong urge to drink, and this craving could worsen their inhibitory deficit, resulting in an inability to suppress their inappropriate drinking behavior.

Interestingly, the ability to suppress inappropriate behavior relies on the operation of control processes that leave their imprint on the corticospinal tract (Derosiere and Duque, 2020). Such effect on the motor output pathway can be investigated in humans by applying single-pulse transcranial magnetic stimulation (TMS) over the primary motor cortex (M1). When applied over M1, TMS elicits motor-evoked potentials (MEPs) in targeted contralateral muscles, and the amplitude of these MEPs provides a temporally precise and muscle-specific measure of the excitability of the corticospinal pathway at the time of stimulation (Bestmann and Duque, 2016). Using this approach, a considerable amount of studies has reported a strong suppression of MEPs during action preparation (Duque et al., 2017). In those studies, participants performed variants of an instructed-delay choice reaction time (RT) task, requiring them to choose between potential finger responses (often the left or right index finger) according to a preparatory cue, and to withhold their response until the onset of an imperative signal. When TMS pulses are applied during the delay period, that is, between the cue and the imperative, MEPs are found to be strongly reduced relative to resting conditions (Hannah and Rothwell, 2017; Lebon et al., 2016; Vassiliadis et al., 2020, 2018). Moreover, this suppression appears to be non-specific and rather global, as it concerns effectors involved in the ongoing task as well as muscles that are task-irrelevant (Greenhouse et al., 2015; Labruna et al., 2019; Quoilin et al., 2016). Critically, this phenomenon is thought to support behavioral inhibition, helping to avoid the emergence of premature or inappropriate responses and more generally, to ensure some sort of impulse control (Derosiere and Duque, 2020; Duque et al., 2017).

Obviously, action preparation also involves excitatory processes that progressively activate the corticospinal neurons coding for the forthcoming movement in a selective way (Cisek and Kalaska, 2005). In instructed-delay choice RT tasks, these excitatory processes start to operate shortly after the preparatory cue has indicated the required response, allowing a fast release of the selected movement after the imperative signal (Davranche et al., 2007; Duque et al., 2010; Sinclair and Hammond, 2008; Tandonnet et al., 2010). Therefore, MEPs probed in a selected effector (i.e. the muscle involved in the forthcoming movement) during the delay period not only reflect the global impulse-control inhibitory influence highlighted above but also this specific excitatory drive. Usually, the inhibitory influences take over the excitatory effects, such that MEPs probed during action preparation are generally smaller, rather than larger, relative to those elicited at rest, even in the selected effector (Duque et al., 2010; Vassiliadis et al., 2018). However, this balance can sometimes be reversed in the selected effector, especially if the tendency to act is particularly strong, such as when the imperative signal is highly expected (van Elswijk et al., 2007) or when the required response concerns the prepotent dominant hand (Quoilin et al., 2016; Wilhelm et al., 2016). In such cases, MEPs elicited in the selected effector may become larger than MEPs elicited in other non-selected or task-irrelevant muscles, given that the latter are only concerned with the inhibitory drive. Therefore, whereas the strength of the tendency to act can be estimated based on MEPs in selected effectors, it is ideal to focus on task-irrelevant effectors, preferentially away from the prime-mover (e.g. in the non-selected hand) to assess the amount of inhibition related to impulse control (Quoilin et al., 2016).

Previously, we have shown that SAUDs display an unusually weak MEP suppression during action preparation, with the extent of the shortage being linked to the propensity to relapse in the subsequent year (Quoilin et al., 2021, 2018). Importantly, these data were acquired in a neutral context, and therefore did not address the impact of an alcohol-related exposure on changes in corticospinal excitability during action preparation. Moreover, it is important to note that MEPs were only probed in task-relevant muscles. Hence, while the lack of MEP suppression in SAUDs was initially interpreted as reflecting a lack of inhibitory influences, an alternative explanation might be that the tendency to act was abnormally high in these subjects, causing an excessive excitatory drive in potential responders that was captured in our MEP measures (Nardone et al., 2019). This hypothesis is supported by the recent observation that binge drinkers exhibit similar MEP suppression as healthy controls when probed in task-irrelevant muscles; the abnormality there only involved a weaker MEP suppression in the selected effector, which may thus reflect an abnormally strong tendency to act rather than deficient inhibition (Grandjean and Duque, 2020).

To address those issues, in the current study, single-pulse TMS was applied over M1 to elicit MEPs in task-relevant and task-irrelevant muscles when detoxified SAUDs, non-treatment seeking HDs and healthy controls (HCs) were performing an instructed-delay choice RT task. The amplitude of MEPs probed in task-relevant muscles was exploited as an indirect measure of the excitatory drive associated with the tendency to act, especially when recorded in the selected effector. Besides, MEPs elicited in task-irrelevant muscles were used to probe inhibitory influences related to impulse control, spared from the excitatory drive associated with the planned response. Note that this is particularly true for task-irrelevant muscles of the non-selected hand because some of the excitatory drive may spread to task-irrelevant muscles of the selected hand (Quoilin et al., 2016). Importantly, to investigate the impact of alcohol exposure on excitatory and inhibitory influences during action preparation, participants were required to perform the task after having been immersed in a neutral or an alcohol-related environment, using virtual reality (VR) immersive videos, and to report their level of subjective craving throughout the experiment. We expected a larger increase in the level of craving following the alcohol-related video in HDs and SAUDs relative to controls, an effect possibly even more pronounced in HDs given that SAUDs inpatients were tested after 17 to 20 days of abstinence. Moreover, we expected that compared to HCs, HDs and SAUDs would show stronger excitatory and reduced inhibitory influences, as evidenced from the pattern of MEPs in the selected task-relevant and non-selected task-irrelevant effectors, respectively, especially when cue-elicited craving is important.

2. Material and methods

2.1. Participants

The study involved a total of 45 participants, including 15 SAUDs (5 women; 50.8 ± 6.5 years old) matched for age, gender and education level with 15 HDs and 15 HCs. SAUDs were diagnosed by a psychiatrist according to DSM-5 criteria and were recruited during the third week of their detoxification program (Saint-Luc University Hospital, Université catholique de Louvain, Brussels, Belgium). SAUDs were tested between day 17 and day 20 of abstinence and were no longer on withdrawal medication. Their mean alcohol consumption before detoxification was 14.2 (standard deviation (SD) = 5.90) alcohol units per day (an alcohol unit = 10 g of pure ethanol), and the mean duration of AUD was 12.1 years (SD = 11.54). To be selected for the study, subjects from the HC and HD groups had to first fill an online questionnaire, including the

Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993). A maximum cut-off score of 7 at the AUDIT was set for the recruitment of HCs, while a score higher or equal to 12 was required to be included in the HD group (Fleming et al., 1991). The mean alcohol consumptions in both groups were 1.1 (SD = 1.06) and 5.2 (SD = 2.15) units per day, respectively. Importantly, subjects from both groups were asked not to drink alcohol on the day of the experiment. Exclusion criteria for the three groups included major neurological or psychiatric disorder, any drug treatment that could influence performance or neural activity (including benzodiazepine), and history of other substance use disorder (except nicotine). Nicotine dependence was more prevalent among SAUDs (n = 6) and HDs (n = 5) than controls (n = 0). Except for one SAUD and one HD, all subjects were right-handed according to the Edinburg Handedness Inventory (Oldfield, 1971). All participants gave written informed consent, following a protocol approved by the Biomedical Ethic Committee of the Saint-Luc University Hospital, Université catholique de Louvain (B403201836840; 2018/22MAI/219). Only HCs and HDs received a financial compensation (€30), in accordance with ethical regulations.

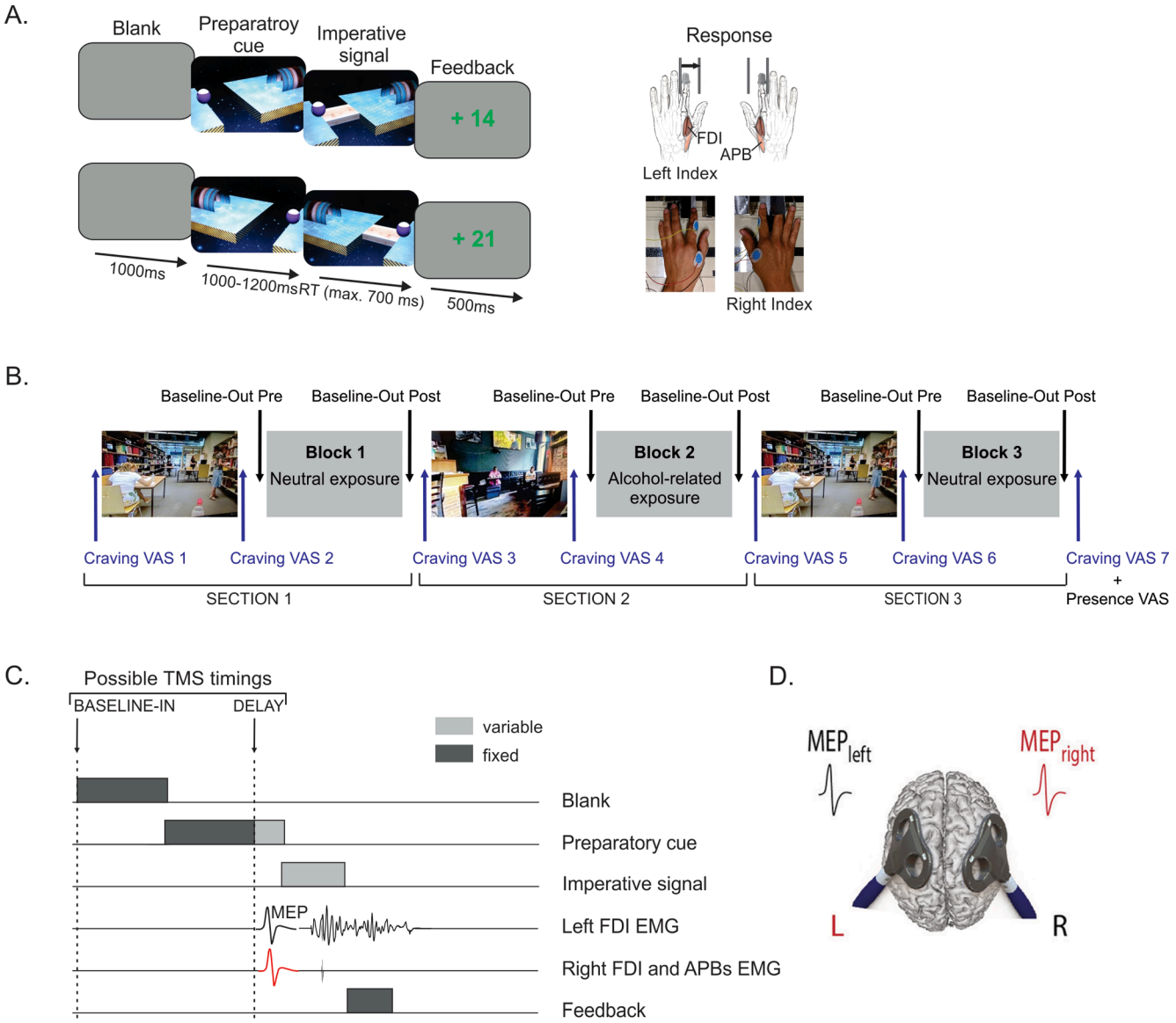

Fig. 1. Experimental procedure. (A) Rolling ball task. Subjects performed an instructed-delay choice reaction time task, requiring them to choose between an abduction movement of the left (non-dominant, upper trace) or right (dominant, lower trace) index finger depending on the position of a preparatory cue (i.e., the ball), and to withhold their response until the onset of an imperative signal (i.e., the bridge). Then, they were required to release their response as fast as possible. Index finger responses were recorded using a home-made response device (schematic representation of the device on the upper trace and actual photography on the lower trace). **(B)** Time course of the experiment. The experiment was divided into three sections, each involving a video and a block of 66 trials of the rolling ball task. The neutral video was shown during the first and the third section while the alcohol-related one was displayed in the middle, during the second section. Besides, the level of subjective craving was measured before and after each video (visual analog scale, VAS) and MEPs were elicited before and after each block to obtain a measure of corticospinal excitability at rest outside the context of the task (BASELINE-OUT). At the end of the experiment, participants rated their level of subjective craving as well as the sense of presence experienced in each virtual environment. **(C)** TMS timings. Transcranial magnetic stimulation (TMS) was used to elicit motor-evoked potentials (MEPs) in the first dorsal interosseous (FDI) and abductor pollicis brevis (APB) muscles of both hands. TMS pulses could occur either at the onset of the blank screen (BASELINE-IN) or 950 ms after the onset of the preparatory cue (DELAY). **(D)** TMS protocol. Two figure-of-eight coil were placed over the subject's primary motor cortex, eliciting near simultaneous MEPs (1 ms delay) in both hands.

2.2. Material

2.2.1. Neutral and alcohol-related virtual environments

During the experiment, participants were immersed in two different environments using a VR system: an alcohol-related video (i.e., a bar) was developed to elicit alcohol craving while a neutral video (i.e., a library) was used as a control exposure. Those videos consisted in two 3D 360° immersive clips lasting for 180 s and displayed in an Oculus Rift VR headset. Importantly, the videos were tested in young social drinkers in a pilot stage of the current experiment, in which we showed that both videos induced a similar virtual experience and that the alcohol-related one significantly enhanced the level of craving. More details about the VR system, the videos and the preliminary tests are provided in the Supplementary Materials.

2.2.2. Self-reported measures

Mood status was measured using French versions of the Spielberger State Trait Anxiety Inventory (STAI Trait and State) (Bruchon-Schweitzer and Paulhan, 1993; Spielberger, 1993) and the Beck Depression Inventory (BDI-II) (Beck et al., 1996). Trait impulsivity was evaluated with the UPPS Impulsive Behavior scale, which is a questionnaire assessing 4 different dimensions of impulsivity, referred to as urgency, lack of premeditation, lack of perseverance and sensation seeking (Billieux et al., 2012; Whiteside et al., 2005). The Immersive Tendencies Questionnaire (ITQ) was used to assess participants' susceptibility to feel immersed in the VR environment (Witmer and Singer, 1998). Finally, the sense of presence experienced in each immersive video as well as the level of subjective craving were evaluated using 100-mm visual analog scales (VAS; score ranging from 0 to 10). More details on the ITQ, the presence and craving VAS are provided in the Supplementary Materials.

2.2.3. Rolling ball task

Participants performed an instructed-delay choice RT task, which was implemented with Matlab 7.5 (Mathworks, Natick, Massachusetts, USA) using the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997). It consisted in a computer-generated "rolling ball" game previously used in other studies, requiring participants to virtually shoot a ball displayed on the computer screen by abducting their left or right index finger (Grandjean et al., 2019; Quoilin et al., 2020; Vassiliadis et al., 2018).

The sequence of events of a typical trial is shown on Fig. 1A. Each trial started with the presentation of a blank screen for 1000 ms. Then, a preparatory cue was displayed, which consisted of a left or right side ball separated from a goal by a gap. This cue allowed participants to prepare their movement but they had to withhold it until the onset of an imperative signal, which appeared after a random delay of 1000 to 1200 ms in the form a bridge connecting the ball and the goal. Participants knew they had to respond as fast as possible once the bridge had appeared, allowing the ball to roll over it and reach the goal. The imperative signal remained visible until a finger response was detected (700 ms max). We purposely varied the duration of the delay between the preparatory cue and the imperative signal to decrease the subjects' tendency to respond prematurely (i.e., before the imperative signal). For the same reason, each block involved some trials in which the bridge did not appear (i.e., catch trials – 6 per block), for which subjects were required not to respond. If they did, the ball fell into the gap. Finally, a feedback score appeared for 500 ms. Correct responses led to positive scores, ranging from 1 to 100 and inversely proportional to the trial's RT ($\text{Score} = \frac{100*(0,8*250)}{(0,8*250)+\left(\frac{RT-(0,8*250)}{10}\right)^{2,4}}$). By contrast, incorrect responses (i.e., responses provided before the imperative, 700 ms after the imperative onset, or with the incorrect finger) were penalized by a negative score (−75). Note that when subjects succeeded not to respond on a catch trial, they received 75 points. The inter-trial interval always lasted for 2300 ms, during which participants were asked to stay still with forearms resting in a semi-flexed position and hands placed palms down on the response device.

2.3. Procedure

All participants came for a single session, which comprised a familiarization period followed by three sections. During familiarization, participants viewed a training immersive video (i.e., an empty lobby displayed for 60 s) and performed a short rolling ball block to become acquainted with the task. Then, each of the three sections involved a phase of virtual exposure followed by one block of the rolling ball task, during which TMS pulses were applied to assess the level of corticospinal excitability. In addition, participants had to complete a craving VAS immediately before and after viewing the video (Fig. 1B). Importantly, the neutral video was always displayed during the first and third sections, while the alcohol-related video was showed in the second one. Furthermore, to strengthen the effect of virtual exposure, soft drinks (Sections 1 and 3) or alcoholic beverages (Section 2) were placed on both sides of the computer screen when the participant was viewing the video, and remained there when he/she was performing the corresponding block. Hence, this design allowed us to assess corticospinal excitability in a neutral condition (Section 1), in an alcohol-related condition (Section 2), and in a neutral condition again, though potentially affected by a persisting craving (Section 3). Finally, the experiment ended with a last measurement of subjective craving and with participants completing a presence VAS for each video.

Each block of the task involved 66 trials during which TMS pulses were applied on both M1 to elicit MEPs in the two hands at once (see TMS protocol below). TMS pulses could be delivered at one of two possible timings (Fig. 1C). To establish a baseline measure of corticospinal excitability, TMS pulses occurred at the onset of the blank screen, eliciting MEPs at rest but in the context of the task ($TMS_{BASELINE\text{-}IN}$; 20 MEPs per block). In other trials, TMS pulses fell 950 ms after the onset of the preparatory cue, when subjects were withholding their response (TMS_{DELAY}; 20 MEPs per side and per block), allowing to assess simultaneously the level of corticospinal excitability during action preparation in a hand selected and non-selected for the forthcoming response, regardless of the responding hand. The remaining trials (6 per block) did not include any TMS pulse, preventing participants from anticipating TMS pulses at TMS_{DELAY} when it had not occurred at $TMS_{BASELINE\text{-}IN}$. Finally, 20 TMS pulses were also applied before and after each experimental block to obtain a baseline measure of corticospinal excitability at rest outside the context of the task ($TMS_{BASELINE\text{-}OUT}$).

2.4. TMS protocol

TMS was delivered using a double-coil method recently developed in our laboratory (Algoet et al., 2018; Grandjean et al., 2018; Wilhelm et al., 2016), where both M1 are stimulated with a 1 ms inter-pulse interval, eliciting MEPs in the dominant (D) and the non-dominant (ND) hands at a near simultaneous time (Fig. 1D). The MEPs obtained using this double-coil approach are comparable to those elicited using single-coil TMS, regardless of the pulse order or the intensity of stimulation (Grandjean et al., 2018; Vassiliadis et al., 2018); here, the first pulse was systematically applied over right M1. Both pulses were delivered through small figure-of-eight coils (wing internal diameter 35 mm), each connected to a stimulator delivering monophasic pulses. The coils were placed tangentially on the scalp with the handle pointing backward and laterally at 45° angle away from the midline, approximatively perpendicular to the central sulcus. For each M1, the optimal coil position for eliciting MEPs in the contralateral first dorsal interosseous (FDI) was identified and marked on a head cap placed on the participant's scalp. This provided the experimenter with a reference mark to accurately hand-hold the coils throughout the experiment (Vandermeeren et al., 2002). The resting motor threshold (rMT) was determined at the hotspot

for each M1 as the minimal TMS intensity required to evoke MEPs of 50 μV peak-to-peak in the relaxed FDI muscle in 5 out of 10 consecutive stimulations. For the dominant M1, the rMT corresponded to 41.4 ± 1.42%, 43.7 ± 2.45% and 42.0 ± 1.80% of the maximum stimulator output in HCs, HDs, and SAUDs, respectively, while it equaled 43.2 ± 1.57%, 44.5 ± 2.38% and 42.3 ± 1.85% for the non-dominant M1 in the corresponding groups. As already evident from the numbers, the rMT did not significantly differ between the three groups ($F_{2,42} = 0.34$; $p = 0.71$; $\eta p^2 = 0.02$) or between the two M1 ($F_{2,42} = 1.51$; $p = 0.23$; $\eta p^2 = 0.03$). The intensity of TMS used throughout the experiment was always set at 115% of the individual rMT for each hemisphere. Note that because finger representations have a large degree of overlap in M1 (Schieber, 2001), TMS pulses applied over the FDI hotspot can also elicit reliable MEPs in other finger muscles. So here, we also recorded MEPs in the abductor pollicis brevis (APB) of both hands, as successfully done in past studies (Grandjean and Duque, 2020; Márquez et al., 2018). This allowed us to obtain measures of corticospinal excitability in both a task-relevant muscle (FDI, index finder abductor) and a task-irrelevant muscle (APB, thumb abductor). If inhibitory influences are altered in HDs and SAUDs, then MEP suppression at TMS_{DELAY} should be weaker in both groups relative to healthy controls and this effect will be most obvious in the task-irrelevant APB of the non-selected hand. Besides, based on the idea that the excitatory drive may also be excessive in HDs and SAUDs, we predicted that these populations would display larger MEPs at TMS_{DELAY} in the task-relevant FDI of the selected hand compared to healthy controls.

2.5. Electromyography (EMG) recording

EMG activity was recorded from surface electrodes (Ambu Blue Sensor NF-50-K Neuroline, Medicotest, Oelstykke, Denmark) placed over the FDI and APB muscles of both hands. The raw EMG signals were amplified (gain, 1 K), bandpass filtered online (10 – 500 Hz, NeuroLog; Digitimer) and digitized at 2000 Hz for offline analysis. EMG data were collected for 3200 ms on each trial, starting always 200 ms before the TMS pulse. Trials with any background EMG activity (root mean square computed in the 200 ms windows preceding the TMS pulse) exceeding 2.5 SD above the mean were removed; this was made for each muscle to prevent contamination of the MEP measurements by significant fluctuations in background EMG (Grandjean et al., 2019; Quoilin et al., 2020). Trials in which subjects made an error were also discarded. The remaining MEPs were then classified according to the muscle and the experimental condition within which they were elicited. For each condition, we excluded trials with peak-to-peak MEP amplitudes exceeding 2.5 SD around the mean. Following data cleaning, a mean of 16.55 ± 1.55, 16.85 ± 0.60 and 16.88 ± 0.64 trials per condition remained to assess corticospinal excitability in HCs, HDs and SAUDs, respectively; the number of remaining trials was not significantly different between the three groups ($F_{2,42} = 0.49$; $p = 0.61$; $\eta p^2 = 0.02$).

2.6. Statistical analyses

Self-reported measures. Analyses of variance (ANOVAs) were performed on demographic and clinical measures, with GROUP (HCs, HDs, SAUDs) as the between-subject factor. To analyze trait impulsivity and immersive tendencies, two multivariate ANOVAs (MANOVAs) were conducted on scores reported on the four subscales of the UPPS questionnaire and the ITQ, respectively, using GROUP (HCs, HDs, SAUDs) as the between-subject factor. Finally, scores at the presence and craving VAS were evaluated using two ANOVAs, with VIDEO (library, bar) or TIMING (1 to 7), respectively, as the within subject-factor, and GROUP (HCs, HDs, SAUDs) as the between-subject factor.

Behavioral data. To analyze behavior during the task, an ANOVA was computed on RTs, with BLOCK (1, 2, 3), RESPONDING-SIDE (ND, D) and TMS-TIMING ($TMS_{BASELINE-IN}$, TMS_{DELAY}) as within-subject factors and GROUP (HCs, HDs, SAUDs) as the between-subject factor.

Corticospinal excitability data. First, we focused on MEPs elicited at rest. The raw amplitudes of FDI and APB MEPs (mV) were analyzed using two separate ANOVAs (uncorrected), with SECTION (1, 2, 3), MEP-SIDE (MEP_{ND}, MEP_{D}) and TMS-TIMING ($TMS_{BASELINE-OUT}$, $TMS_{BASELINE-IN}$) as within-subject factors and GROUP (HCs, HDs, SAUDs) as the between-subject factor. Second, we considered MEPs at TMS_{DELAY}; those MEPs were expressed in percentage of MEPs elicited at $TMS_{BASELINE-IN}$. As our first goal was to characterize the evolution of these percentage MEPs across the three blocks in each group and each muscle, we ran 6 separate ANOVAs (uncorrected) using BLOCK (1, 2, 3), RESPONDING-SIDE (ND, D) and CONDITION (Selected, Non-selected) as within-subject factors. Additionally, to assess the presence of preparatory changes in corticospinal excitability in each condition, one-sample t-tests (Bonferroni-corrected) were used to compare these percentage values to a constant value of 100 (i.e., to $TMS_{BASELINE-IN}$). Finally, to specifically address our hypotheses regarding the strength of excitatory and inhibitory influences across the three groups, we performed two separate ANOVAs (uncorrected) on MEPs at TMS_{DELAY} in the selected FDI, which best capture the excitatory drive associated with the tendency to act (1), and on MEPs in the APB of the non-selected hand, which best capture the inhibitory drive related to impulse control (2) (Grandjean and Duque, 2020; Quoilin et al., 2016). Those data were analyzed using BLOCK (1, 2, 3) and MEP-SIDE (MEP_{ND}, MEP_{D}) as within-subject factors and GROUP (HCs, HDs, SAUDs) as the between-subject factor.

Relationships between impulsivity, craving and preparatory changes in corticospinal excitability. First, to test for a potential link between trait impulsivity and preparatory changes, Pearson's correlations were performed on the whole sample between scores at the four subscales of the UPPS questionnaire and measures of the excitatory and inhibitory drive (percentage MEPs at TMS_{DELAY} probed during Block 1 in the selected ND and D FDI and the non-selected ND and D APB). Second, we ran a series of additional analyses to investigate the link between craving and both trait impulsivity and preparatory changes. As HDs were the only group to self-report craving, those analyses were performed in this group specifically. We focused on two craving-related variables: the global craving score at the beginning of the experiment (i.e., scores at VAS 1) and the craving induced by the alcohol-related exposure ($\Delta_{craving}$ = Scores at VAS 4 - Scores at VAS 3; see Fig. 1B). On the one hand, the potential relationship between craving and trait impulsivity was assessed by performing Pearson's correlations between these variables and the scores at the four subscales of the UPPS. On the other hand, we ran Pearson's correlations between craving at the beginning of the experiment and preparatory changes before any alcohol-related exposure (percentage MEPs at TMS_{DELAY} probed during Block 1 in the selected FDIs and the non-selected APBs) as well as between $\Delta_{craving}$ and changes in the excitatory and inhibitory drive following the alcohol-related exposure (Δ_{MEPs} = percentage MEPs at TMS_{DELAY} during Block 2 – percentage MEPs at TMS_{DELAY} during Block 1 for the selected FDIs and the non-selected APBs). Bonferroni corrections were applied to control for multiple comparisons.

Following the ANOVAs, effect sizes were provided (partial eta-square) and the Fisher's Least Significant Difference (LSD) method was used to run post-hoc comparisons. Analyses were carried out using Statistica 10 (StatSoft, Cracow, Poland). The statistical significance was set at $p < 0.05$.

3. Results

3.1. Self-reported measures

Demographic and current clinical status. As illustrated in Table 1, subjects from the three groups were fully matched for age ($F_{2,42} = 0.001$; $p = 0.99$; $\eta p^2 = 0.00$) and education level ($F_{2,42} = 0.385$; $p = 0.68$; $\eta p^2 = 0.02$). By contrast, groups differed in terms of state anxiety ($F_{2,42} = 0.55$; $p < 0.01$; $\eta p^2 = 0.21$), trait anxiety ($F_{2,42} = 10.62$; $p < 0.001$; $\eta p^2 =$

Table 1
Demographic and self-reported measures in healthy controls (HCs), heavy drinkers (HDs), and patients with severe alcohol use disorders (SAUDs) [Mean *(SE)*].

Demographic and psychopathological measures	HCs (n = 15)	HDs (n = 15)	SAUDs (n = 15)	Group comparisons
Age ^{NS}	50.7 *(1.92)*	50.9 *(1.86)*	50.8 *(1.67)*	
Education level[1] ^{NS}	15.7 *(0.64)*	16.1 *(0.74)*	15.3 *(0.71)*	
State anxiety **	27.1 *(1.70)*	35.6 *(2.54)*	42.2 *(4.63)*	SAUDs > HCs
Trait anxiety ***	35.3 *(1.76)*	40.47 *(2.36)*	50.8 *(2.99)*	SAUDs > HDs, HCs ; HDs > HCs
BDI **	4.3 *(0.99)*	10.3 *(2.07)*	19 *(3.93)*	SAUDs > HDs, HCs ; HDs > HCs
AUDIT ***	4.3 *(0.55)*	16.8 *(1.08)*	28.8 *(1.57)*	SAUDs > HDs, HCs ; HDs > HCs
Trait impulsivity: UPPS Scale **				
Urgency ***	24.9 *(1.47)*	29.7 *(1.30)*	33.4 *(1.42)*	SAUDs, HDs > HCs
Lack of premeditation ^{NS}	20.5 *(0.76)*	24.6 *(1.59)*	22.1 *(1.41)*	
Lack of perseverance ^{NS}	18.0 *(0.95)*	20.2 *(1.07)*	18.7 *(1.00)*	
Sensation seeking ^{NS}	29.7 *(2.30)*	31.1 *(1.71)*	29.5 *(2.24)*	
Immersive Tendencies Questionnaire ^{NS}				
Focus	27.8 *(1.00)*	24.2 *(1.19)*	23.5 *(1.77)*	
Involvement	17.3 *(1.71)*	17.6 *(1.54)*	14.9 *(0.87)*	
Emotions	13.5 *(1.37)*	13.5 *(0.98)*	14.4 *(1.11)*	
Games	7.4 *(0.97)*	7.8 *(0.80)*	6.8 *(1.19)*	
Presence VAS ^{NS}				
Neutral video	5.8 *(0.52)*	5.0 *(0.47)*	5.0 *(0.71)*	
Alcohol-related video	5.5 *(0.52)*	5.3 *(0.48)*	5.3 *(0.62)*	

[1]The education level reflects the number of years of education completed since starting primary school. BDI = Beck Depression Inventory; AUDIT = Alcohol Use Disorders Identification Test; VAS = Visual Analog Scale; NS = non-significant; **p < 0.01; ***p < 0.001.

0.34), and depression ($F_{2,42} = 7.87$; $p < 0.01$; $\eta p^2 = 0.27$), with SAUDs reporting the highest levels on each scale. Finally, and as expected, the average AUDIT score was higher in SAUDs relative to both groups ($p < 0.001$), while it was larger in HDs than in HCs ($p < 0.001$).

Trait impulsivity. The MANOVA performed on scores at the UPPS scale showed a significant main effect of GROUP ($\lambda_{8,78} = 0.60$; $p < 0.01$; $\eta p^2 = 0.22$), due to higher scores on the urgency subscale in SAUDs and HDs relative to controls ($p < 0.05$; Table 1), while scores in the two former groups were not significantly different ($p = 0.07$).

Immersive tendencies. The MANOVA computed on scores at the ITQ revealed that immersive predispositions were not significantly different among the three groups ($\lambda_{8,74} = 0.80$; $p = 0.38$; $\eta p^2 = 0.10$; Table 1).

Effects of the virtual exposure. The mean scores on presence VAS are reported in Table 1. Analyses revealed neither a significant main effect of GROUP ($F_{2,42} = 0.30$; $p = 0.74$; $\eta p^2 = 0.01$) or VIDEO ($F_{2,42} = 0.34$; $p = 0.56$; $\eta p^2 = 0.01$), nor a GROUP × VIDEO interaction ($F_{2,42} = 1.36$; $p = 0.27$; $\eta p^2 = 0.06$), indicating that the sense of presence experienced in each immersive video was similar, regardless of the group. By contrast, the global craving score was significantly different among the three groups ($F_{2,42} = 5.32$; $p < 0.01$; $\eta p^2 = 0.20$): it was higher in HDs than in SAUDs and controls ($p < 0.05$), but did not differ between the two latter ($p = 0.52$). Moreover, the main effect of TIMING was significant ($F_{6,252} = 3.26$; $p < 0.01$; $\eta p^2 = 0.07$), and this effect depended on GROUP (GROUP × TIMING interaction; $F_{12,252} = 3.29$; $p < 0.001$; $\eta p^2 = 0.14$). As such, in HDs, scores on craving VAS started to slightly increase right before the alcohol-related exposure (i.e., VAS 3 vs VAS 1; $p < 0.05$), continued to further increase with the bar video (i.e., VAS 4 vs VAS 3; $p < 0.05$), and then remained steady until the end of the experiment (VAS 5–7 vs VAS 4; all $p > 0.17$), contrary to SAUDs and HCs in whom subjective craving stayed constant (all $p > 0.06$; Fig. 2). In other words, our procedure successfully induced subjective craving, but this effect only arose in HDs.

3.2. Behavioral data

The RTs measured during the rolling ball task are shown in Fig. 3. Analyses revealed a significant effect of BLOCK ($F_{2,84} = 7.94$; $p < 0.001$; $\eta p^2 = 0.16$), participants becoming faster to respond during Blocks 2 and 3 than during Block 1 ($p < 0.001$). Furthermore, the factor TMS-TIMING was significant ($F_{1,42} = 26.39$; $p < 0.001$; $\eta p^2 = 0.39$): RTs were shorter at TMS_{DELAY} than at $TMS_{BASELINE\text{-}IN}$, consistent with many reports showing that a TMS pulse applied close to the imperative signal can speed up the release of a motor response (Greenhouse et al., 2015; Vassiliadis et al., 2018). Besides, neither the factor GROUP ($F_{2,42} = 2.45$; $p = 0.10$; $\eta p^2 = 0.10$), nor the factor RESPONDING-SIDE ($F_{1,42} = 0.22$; $p = 0.64$; $\eta p^2 = 0.01$), or any of the interactions were significant (all $F < 1.71$ and all $p > 0.15$). Hence, HCs, HDs and SAUDs performed equally in the task.

3.3. Corticospinal excitability data

MEPs elicited at $TMS_{BASELINE\text{-}OUT}$ and $TMS_{BASELINE\text{-}IN}$

As evident on Fig. 4, MEPs acquired at rest were globally larger at $TMS_{BASELINE\text{-}IN}$ than at $TMS_{BASELINE\text{-}OUT}$, and this TMS-TIMING effect concerned both the FDI ($F_{1,42} = 54.61$; $p < 0.001$; $\eta p^2 = 0.57$) and the APB ($F_{2,42} = 11.26$; $p < 0.01$; $\eta p^2 = 0.22$), despite the fact that the latter muscle was task-irrelevant. Hence, consistent with prior works (Labruna et al., 2019; Quoilin et al., 2019; Vassiliadis et al., 2020), the level of corticospinal excitability was globally higher in the context of the task than at complete rest. Moreover, MEP amplitudes tended to be larger at the end of the experiment. This was supported by the significant effect of the factor SECTION ($F_{2,80} = 5.01$; $p < 0.01$; $\eta p^2 = 0.11$) on MEPs elicited in the APB, which were greater during the last block relative to the first one ($p < 0.01$). Such an increase was also observed in the FDI, although

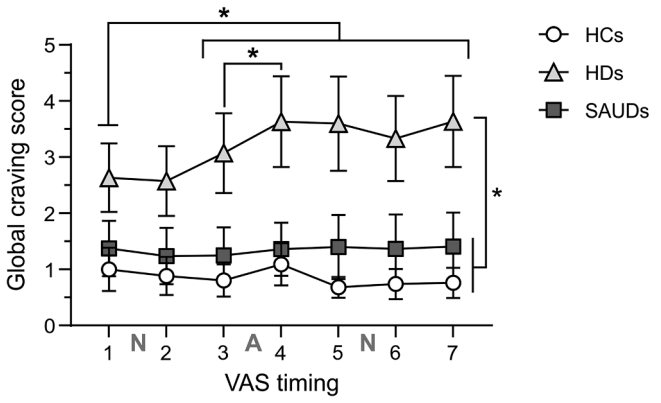

Fig. 2. Level of subjective craving throughout the experiment. Global scores at the craving visual analog scales (VAS) self-completed at different time points (VAS 1 to 7, see Fig. 1B) are shown for HCs (white), HDs (light grey) and SAUDs (dark grey). The neutral video (N) was displayed between VAS 1 and 2, as well as between VAS 5 and 6, while the alcohol-related video (A) was shown between VAS 3 and 4. Please note the significant increase induced by the alcohol-related video in HDs. *p < 0.05 : significantly different.

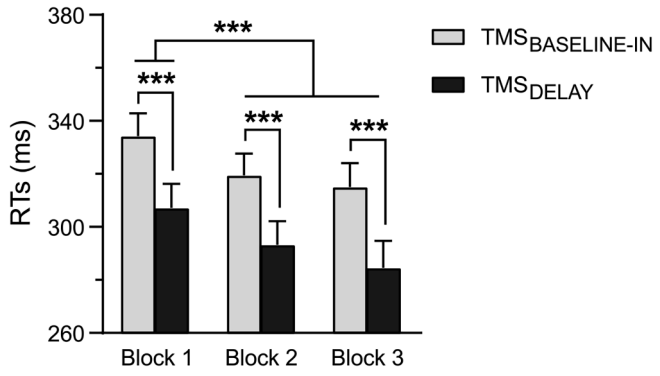

Fig. 3. Reaction times (RTs) during the rolling ball task. The RTs are shown during the three blocks for trials in which the TMS pulses were applied either at baseline ($TMS_{BASELINE-IN}$, light grey) or during action preparation (TMS_{DELAY}, dark grey). Data from the three groups and for responses performed with both hands were comparable and thus pooled together. ***p < 0.001: significantly different, such as indicated by the main effect of the factor TMS-TIMING and the post-hoc tests performed following the significant main effect of the factor BLOCK.

the effect did not reach significance ($F_{2,84} = 2.66$; $p = 0.08$; $\eta p^2 = 0.06$). No other main effect or interaction was significant (FDI: all $F < 1.48$ and all $p > 0.12$; APB: all $F < 2.54$ and all $p > 0.11$), indicating that those effects were present in both hands and in the three groups.

4. Meps elicited at TMS_{DELAY}

A glimpse at Fig. 5 provides a global picture of preparatory changes in corticospinal excitability underwent by the FDI - i.e., the task-relevant muscle - over the blocks in the three groups of subjects. Unsurprisingly, in HCs (Fig. 5A), MEPs probed at TMS_{DELAY} were reduced relative to baseline, reflecting the presence of strong inhibitory influences when subjects were preparing and withholding their finger response. As shown by the t-tests (comparisons to a constant value of 100; $\alpha = 0.05/12$), this MEP suppression was particularly noticeable when the muscle was not selected for the forthcoming response, consistent with the occurrence of excitatory inputs neutralizing part of this effect in the selected conditions (Quoilin et al., 2016; Wilhelm et al., 2016). Furthermore, the BLOCK × RESPONDING-SIDE interaction was significant ($F_{2,28} = 3.52$; $p < 0.05$; $\eta p^2 = 0.20$), revealing a global strengthening of the MEP suppression when responses were prepared with the dominant hand. Accordingly, MEPs elicited during dominant hand trials were smaller in Block 3 relative to the first two blocks (both $p < 0.05$), regardless of whether they were probed in a selected (D hand) or non-selected (ND hand) condition.

HDs also displayed a significant suppression of MEPs in the FDI (Fig. 5B). However, here, the suppression was systematically absent when MEPs were probed in the selected dominant effector (all $|t| < 1.46$ and all $p > 0.16$; i.e. $> 0.05/12$). This was confirmed by the RESPONDING-SIDE × CONDITION interaction ($F_{1,14} = 5.48$; $p < 0.05$; $\eta p^2 = 0.28$), showing that MEPs probed during dominant hand trials were larger in the selected setting (D hand) relative to the non-selected one (ND hand). Hence, it seems that the excitatory drive was particularly strong in HDs when the forthcoming response entailed the dominant hand. Interestingly, an excessive excitatory drive in the selected dominant hand was also observed in SAUDs (RESPONDING-SIDE × CONDITION interaction; $F_{1,14} = 8.73$; $p < 0.05$; $\eta p^2 = 0.38$, see Fig. 5C). Moreover, a specificity in this group is that we had to wait for the last block before MEPs became significantly suppressed, suggesting that this effect needed more practice to emerge. Critically, in view of the lack of significant main effect of BLOCK in the three groups (all $F < 2.56$ and all $p > 0.09$), our results also show that preparatory changes in corticospinal excitability following the alcohol-related exposure were not significantly different from those observed following exposure in the neutral condition.

The data obtained in the APB are shown in Fig. 6. In line with the fact that MEP suppression during action preparation is a global phenomenon, also covering task-irrelevant muscles (Duque et al., 2017), APB MEPs probed at TMS_{DELAY} in HCs were also suppressed relative to baseline (Fig. 6A), even though the t-tests show that this effect was more apparent later during the experiment. Besides, similar to the FDI, this strengthening depended on the responding side (BLOCK × RESPONDING-SIDE interaction; $F_{2,28} = 9.70$; $p < 0.001$; $\eta p^2 = 0.41$). As such, it was particularly manifest for dominant hand trials, with MEPs probed during Block 3 being drastically smaller than those recorded during the two first blocks (both $p < 0.001$), while this effect was slighter for responses involving the non-dominant hand (Block 3 vs Block 1; $p < 0.05$). Critically, here, the t-tests indicate that MEP suppression was also largely present in HDs (Fig. 6B), while MEPs probed in SAUDs were not significantly reduced relative to baseline in any of the conditions (Fig. 6C). Moreover, in agreement with the fact that MEPs probed in the APB are preserved from excitatory influences at play in the selected task-relevant muscle, the RESPONDING-SIDE × CONDITION interaction was not significant either in HDs ($F_{1,14} = 0.18$; $p = 0.68$; $\eta p^2 = 0.01$) or in SAUDs ($F_{1,14} = 0.03$; $p = 0.88$; $\eta p^2 = 0.00$). Finally, and as evident on the figure, those data reveal that the alcohol-related exposure had no impact on the level of preparatory inhibitory influences.

To summarize these results, a significant MEP suppression was observed both in task-relevant and task-irrelevant muscles in HCs, while this phenomenon seemed less obvious in HDs and SAUDs. Indeed, when

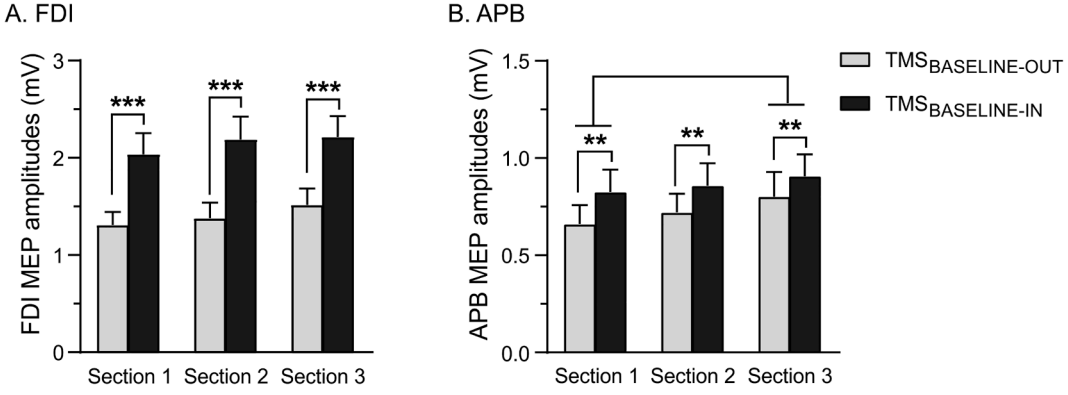

Fig. 4. Measures of corticospinal excitability at rest. Raw amplitude of motor-evoked potentials (MEPs, in mV) recorded either outside ($TMS_{BASELINE-OUT}$, light grey) or within ($TMAS_{BASELINE-IN}$, dark grey) the blocks are shown for **(A)** the first dorsal interosseous (FDI) and **(B)** the abductor pollicis brevis (APB). Data are collapsed across the three groups and both hands. Note that MEPs at $TMS_{BASELINE-OUT}$ in Section 1, 2 and 3 comprised MEPs elicited before and after each corresponding block. **p < 0.01 and ***p < 0.001: significantly different.

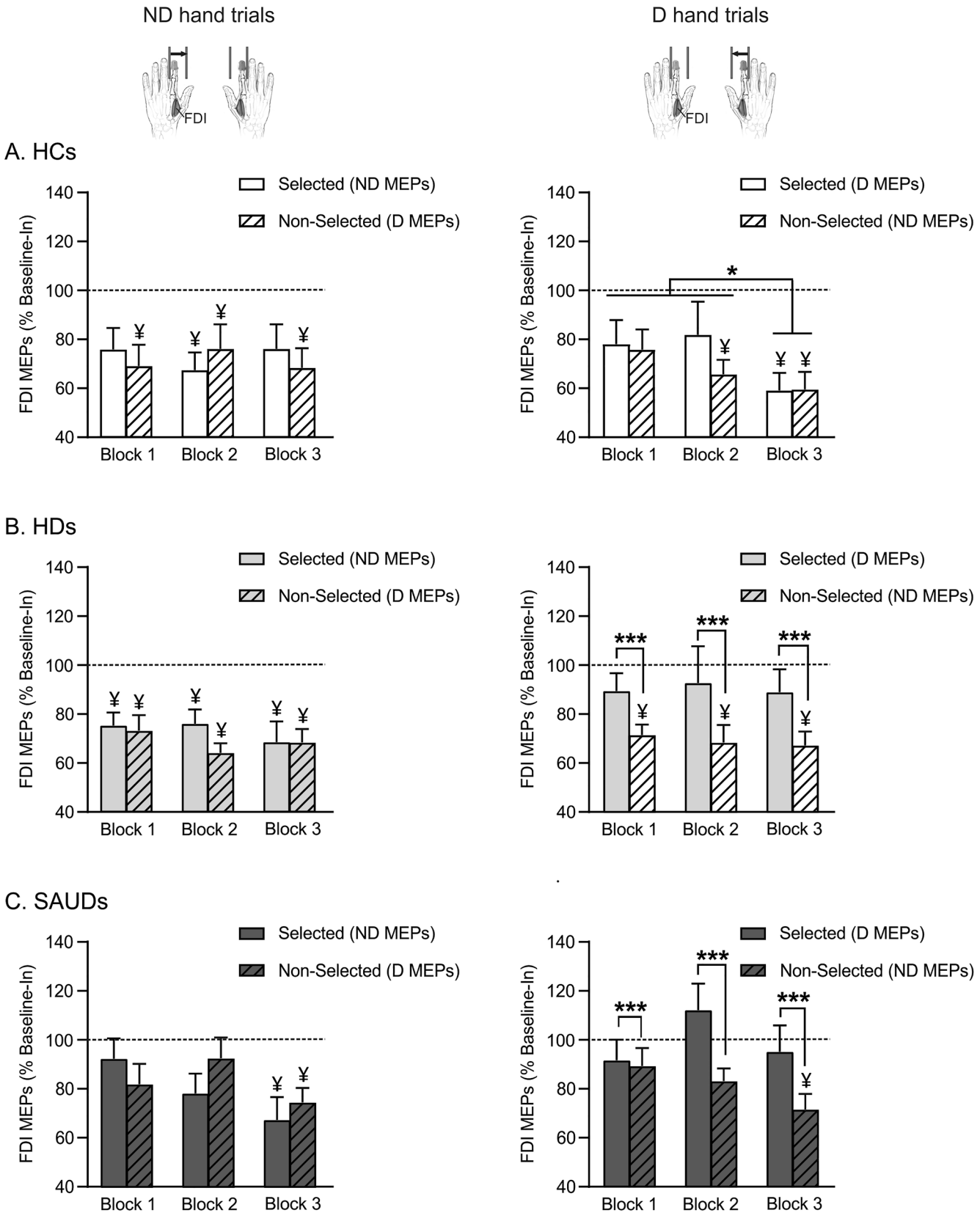

Fig. 5. Measures of preparatory changes in corticospinal excitability in the task-relevant first dorsal interosseous (FDI) muscles. The amplitudes of motor-evoked potentials (MEPs) recorded during the three blocks at TMS_{DELAY}, expressed in percentage of MEPs elicited at $TMS_{BASELINE\text{-}IN}$, are shown for a FDI which was either selected (open bars) or non-selected (dashed bars) for the forthcoming response in HCs **(A)**, HDs **(B)** and SAUDs **(C)**. The data are depicted separately for non-dominant (ND, left panel) and dominant (D, right panel) hand trials. ¥ = significantly different from MEPs probed at $TMS_{BASELINE\text{-}IN}$ ($p < 0.05/12$). **$p < 0.01$: significantly different.

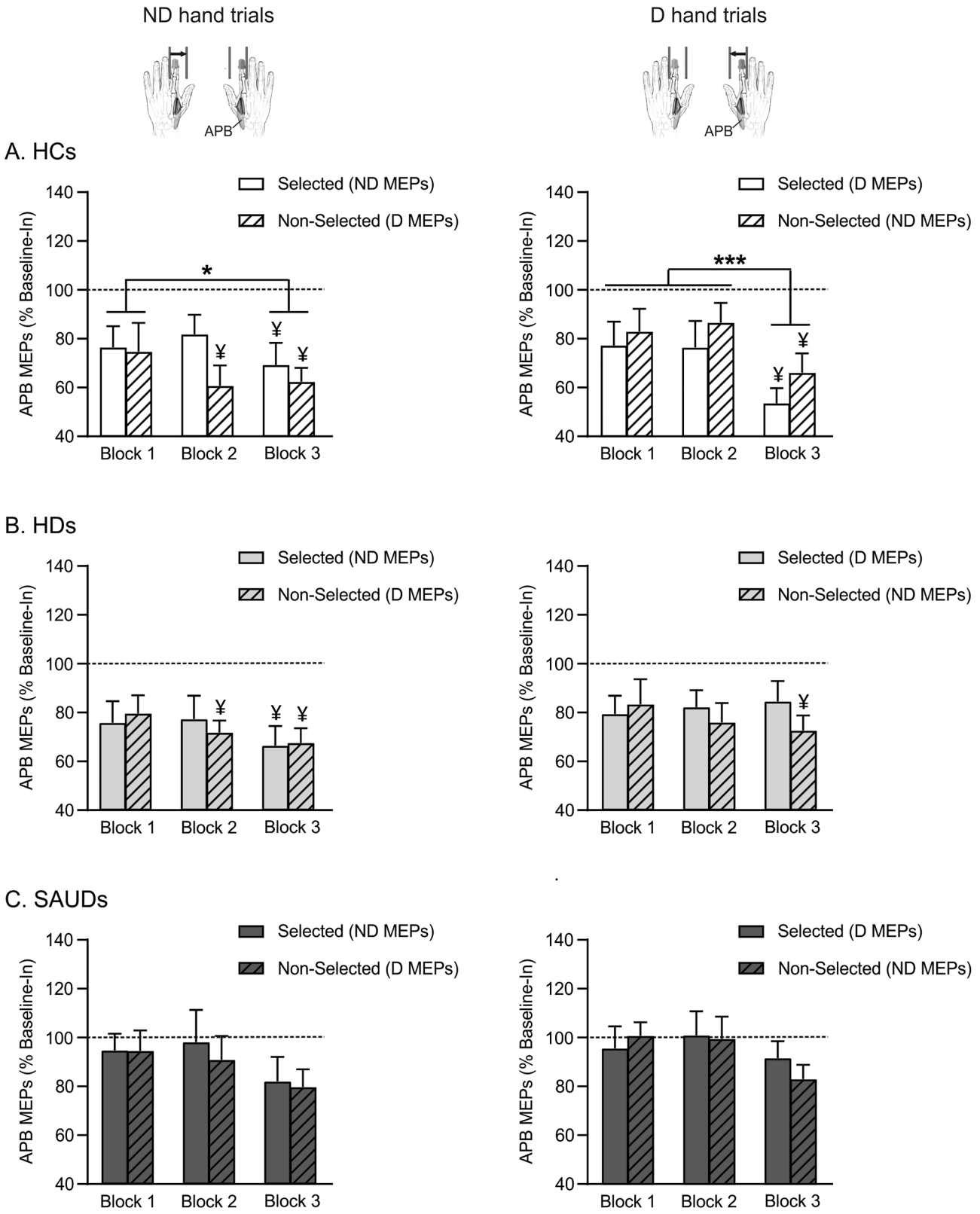

Fig. 6. Measures of preparatory changes in corticospinal excitability in the task-irrelevant abductor pollicis brevis (APB) muscles. The amplitudes of motor-evoked potentials (MEPs) recorded during the three blocks at TMS_{DELAY}, expressed in percentage of MEPs elicited at $TMS_{BASELINE\text{-}IN}$, are shown for the APB, in a hand that was either selected (open bars) or non-selected (dashed bars) for the forthcoming response in HCs **(A)**, HDs **(B)**, and SAUDs **(C)**. The data are depicted separately for non-dominant (ND, left panel) and dominant (D, right panel) hand trials. ¥ = significantly different from MEPs probed at $TMS_{BASELINE\text{-}IN}$ ($p < 0.05/12$). * $p < 0.05$ and ** $p < 0.01$: significantly different.

probed in the task-relevant muscle, the MEP suppression was systematically absent in the dominant selected hand in both groups. In addition, a lack of suppression in the task-irrelevant muscle was observed in SAUDs. In other words, based on these results, we could assume that HDs and SAUDs present a particularly high excitatory drive in relation to a cued response with the dominant hand, to which would add up a lack of inhibitory influences in the SAUD group.

In order to directly address these hypotheses, further analyses aimed at directly comparing the three groups by focusing firstly on conditions in which MEPs reflected excitatory inputs- i.e., the selected FDI-, and secondly on conditions in which MEPs more specifically reflected inhibitory influences - i.e., the non-selected APB. Interestingly, analyses performed on the selected FDI revealed a significant GROUP × MEP-SIDE interaction ($F_{2,42} = 3.19$; $p < 0.05$; $\eta p^2 = 0.13$; Fig. 7A). That is, while there was no significant difference between the three groups for MEPs probed in the non-dominant FDI (all $p > 0.64$), differences were present for MEPs elicited in the dominant FDI. In particular, SAUDs displayed larger MEPs than controls ($p < 0.05$), whereas HDs had intermediate values, not differing either from SAUDs ($p = 0.50$) or from HCs ($p = 0.21$). Moreover, when we considered MEPs in the non-selected APB, we obtained a main effect of GROUP ($F_{2,42} = 4.08$; $p < 0.05$; $\eta p^2 = 0.16$) regardless of the side (GROUP × MEP-SIDE interaction; $F_{2,42} = 0.19$; $p = 0.82$; $\eta p^2 = 0.01$; Fig. 7B). Here, MEPs were significantly less suppressed in SAUDs relative to both HDs and HCs ($p < 0.05$), while there was no significant difference between the two latter groups ($p = 0.70$).

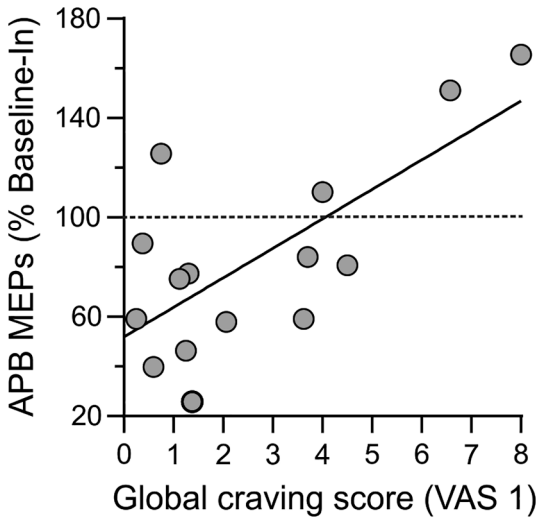

Fig. 8. Relationships between the level of craving and preparatory changes in corticospinal excitability at the beginning of the experiment in heavy drinkers (HDs). The figure depicts the positive correlation between scores on the first craving visual analog scale (VAS) and MEPs probed at TMS_{DELAY} during Block 1, expressed in percentage of MEPs probed at $TM_{BASE-LINE-IN}$, in the non-selected APB preceding dominant hand responses. hand responses. Please note however that this correlation was largely driven by two participants, but none of these two subjects could be considered as an outlier.

4.1. *Relationships between impulsivity, craving and preparatory changes in corticospinal excitability.*

First, correlational analyses were performed between trait impulsivity and preparatory changes. Consistent with previous works (Quoilin et al., 2021, 2018), results did not show any significant relationship (all $-0.15 < r < 0.14$ and $p > 0.34$; i.e. $> 0.05/16$), confirming that trait impulsivity and changes in corticospinal excitability during action preparation represent different facets of inhibitory control. Then, we investigated the relationship between craving and both trait impulsivity and preparatory changes. As the HD group was the only one to report a significant level of subjective craving, analyses were specifically performed on these subjects. Regarding trait impulsivity, we did not find any significant correlation between the scores at the four subscales of the UPPS and craving at VAS 1 or $\Delta_{craving}$ (all $-0.13 < r < 0.51$ and $p > 0.05$; i.e. $> 0.05/8$). By contrast, analyses performed on preparatory changes revealed that the level of craving when starting the experiment (i.e., score at VAS 1) positively correlated with MEPs at TMS_{DELAY} in Block 1 (Fig. 8). That is, the higher the level of craving at the beginning of the experiment, the higher the MEPs at TMS_{DELAY} in the first block. Critically, this relationship was only found for MEPs probed in the APB of the non-selected hand during dominant hand trials ($r = 0.70$; $p < 0.00625$; i.e. $< 0.05/8$), suggesting that a higher craving was specifically related to weaker preparatory inhibitory influences in HDs. Finally, results did not show any significant correlation (all $-0.11 < r < 0.46$ and $p > 0.08$; i.e. $> 0.05/8$) between $\Delta_{craving}$ (i.e., scores at VAS 4 - Scores at VAS 3) and Δ_{MEPs} (i.e., MEPs at TMS_{DELAY} during Block 2 – MEPs at TMS_{DELAY} during Block 1). Hence, even when a craving was elicited by the alcohol-related exposure, it was not associated with a change in the level of corticospinal excitability during action preparation.

5. Discussion

Behaving in an appropriate manner relies on control processes, distributed across the brain, which properly shape the activity of the motor output pathway. In particular, action preparation entails profound modulatory changes within the corticospinal tract (Derosiere and Duque, 2020; Duque et al., 2017). On the one hand, excitatory processes prepare the motor system for the forthcoming action; the stronger this excitatory drive, the greater the urge to act. On the other hand, strong inhibitory influences operate in parallel, allowing to suppress inappropriate actions and thus ensuring some sort of impulse control. Because an impairment in these processes could foster inappropriate drinking behavior, the present study considered excitatory and inhibitory

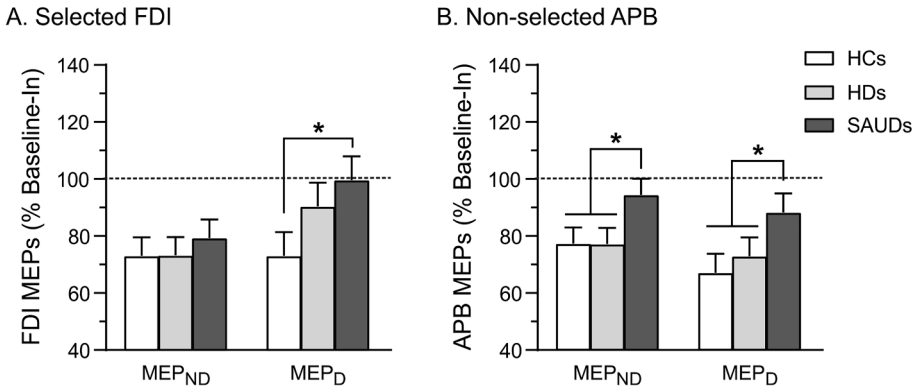

Fig. 7. Measures of preparatory changes in corticospinal excitability in the selected first dorsal interosseous (FDI; A) and in the non-selected abductor pollicis brevis (APB; B) of the non-dominant (MEP_{ND}) and the dominant (MEP_D) hands. Those conditions were chosen to more directly compare excitatory and inhibitory influences, respectively, between HCs (white), HDs (light grey), and SAUDs (dark greys). The illustrated data are pooled across the three blocks. *p < 0.05: significantly different.

influences at play during action preparation in detoxified SAUDs and non-treatment seeking HDs, as well as the impact of an alcohol-related exposure on these mechanisms. Our data indicate that both groups displayed a particularly high excitatory drive when compared to healthy participants, suggesting an abnormally strong urge to act. As for inhibitory influences, they were found to be deficient in SAUDs but not in HDs. Finally, contrary to our original belief, exposure to an alcohol-related environment did not seem to affect preparatory changes in corticospinal excitability in any of the groups.

In healthy subjects, the amplitude of MEPs was globally lower during the delay period than at rest, consistent with substantial TMS work showing a strong suppression of corticospinal excitability during action preparation (Grandjean et al., 2019; Labruna et al., 2019; Lebon et al., 2016; Vassiliadis et al., 2020, 2018). This suppression concerned both task-relevant and task-irrelevant muscles, including the selected effector. Hence, strong inhibitory influences were manifest in healthy subjects, and were deep enough to overcome the excitatory drive associated with the planned response. The latter was not true for HDs, in whom MEP suppression was systematically absent when probed in the selected effector, especially in the dominant hand. Importantly, this lack of suppression seems to result from an excessive excitatory drive, as task-irrelevant muscles displayed a normal level of MEP suppression (comparable to that found in HCs), suggesting perfectly normal inhibitory influences in these subjects. In other words, the current findings suggest that HDs present an abnormally strong tendency to act, which specifically manifests when the forthcoming response entails their dominant hand. If this manual asymmetry might seem surprising at first sight, it is in fact highly consistent with past studies showing that increased readiness to initiate actions is often more prominent in effectors of the dominant hand (Mars et al., 2007; Quoilin et al., 2016; van den Hurk et al., 2007; Wilhelm et al., 2016). Notably, MEPs in SAUDs also uncovered excessive excitatory influences. Hence, unsurprisingly, there is an increased urge to act in this population too. However, in addition to that, SAUDs displayed a lack of inhibitory influences, as the task-irrelevant MEP suppression was also weaker in these patients. Thus, our findings corroborate the shortage of MEP suppression previously reported in those patients (Quoilin et al., 2021, 2018) and allow to directly link this observation to deficiencies concerning both excitatory and inhibitory modulatory drives directed at the motor system during action preparation.

Given the observation of deficient inhibition in SAUDs, but not in HDs, one might posit that a deficit in preparatory inhibition is a hallmark of more severe forms of AUD. In line with this hypothesis, we have previously shown that the extent of the defect is related to the subsequent propensity to relapse, suggesting that it represents a biomarker of addiction severity (Quoilin et al., 2018). Besides, here, an interesting relationship was found between the level of craving at the beginning of the experiment and the degree of MEP suppression probed in task-irrelevant muscles. That is, HDs with a higher level of craving at baseline, who may thus be further on the path towards AUD, also displayed a weaker inhibitory drive. While this result should really be taken with caution due to the small sample sizes, it is consistent with other studies relating craving intensity and inhibitory abilities (Naim-Feil et al., 2014; Papachristou et al., 2012b, 2013). By contrast, because a higher excitatory drive was observed both in HDs and SAUDs, a greater tendency to act might represent a common feature of hazardous drinking. Interestingly, young binge-drinkers, who are also characterized by unhealthy drinking habits (Lannoy et al., 2019), present a pattern of MEP changes remarkably similar to the one reported in HDs (Grandjean and Duque, 2020). As such, they have been found to show a drastically weaker MEP suppression when probed in selected effectors, despite a normal suppression in task-irrelevant muscles (Grandjean and Duque, 2020).

Based on the finding that an enhanced excitatory drive concerns binge-drinkers, HDs and SAUDs, it would be tempting to assume that a higher tendency to act would represent a vulnerability factor, present before any alcohol consumption and predisposing individuals to excessive drinking. In agreement with this idea, scores obtained on the UPPS scale revealed that both HDs and SAUDs had higher trait impulsivity than controls. Even more strikingly, scores were particularly high on the urgency subscale, which reflects the tendency to act rashly (Whiteside et al., 2005). Though, note that scores did not significantly correlate with the level of preparatory changes. Critically, a greater trait impulsivity, which is recognized as a risk factor for developing AUD (Dick et al., 2010), represents a stable personality characteristic. On the other hand, the lack of inhibitory drive, evidenced only in SAUDs, would rather be a consequence of chronic heavy drinking. Several lines of evidence support this hypothesis. First, chronic alcohol consumption has important neurotoxic effects, with the most pronounced damage reported in regions underpinning impulse control, such as the frontal lobes and the basal ganglia (Chanraud et al., 2007; Fritz et al., 2019), and the degree of brain atrophy correlates with the amount of alcohol previously consumed (Rolland et al., 2020). Moreover, we have shown that a weaker MEP suppression during action preparation was associated with a lower cortical thickness in medial frontal regions (Quoilin et al., 2021), while patients suffering from a behavioral, substance-free, addiction, had a normal pattern of MEP suppression (Quoilin et al., 2020). Finally, here, HDs reported a considerably lower alcohol consumption than SAUDs, which could explain the lack of visible impairment in the strength of inhibitory influences. Even so, it is still unclear why HDs, despite years of heavy consumption, have not developed a more severe form of AUD. It might be that they were less sensitive to the neurotoxic effects of alcohol, or that they had particularly high initial preparatory inhibition, which, in both cases, would have acted as a protective factor. Ideally, longitudinal studies, combining measures of MEP suppression, brain morphometry and alcohol consumption, should be performed to shed light on this question.

As one of our main goals was to evaluate the impact of cue-elicited craving on MEP suppression, VR videos were used to immerse participants in an alcohol-related environment. Such as expected, the exposure significantly increased the level of self-reported craving in HDs. By contrast, it did not affect craving intensity in controls and detoxified SAUDs, even though the sense of presence and immersive predispositions were similar in the three groups. Even more surprisingly, SAUDs did not report any craving throughout the experiment: scores were comparable to controls, and radically lower than HDs. Yet, other studies have shown that a significant proportion of patients are not sensitive to an alcohol-related exposure (Hernández-Serrano et al., 2020; Litt et al., 2000; Papachristou et al., 2013), and that detoxified inpatients usually report lower levels of craving than continuing substance users (Wertz and Sayette, 2001). This discrepancy might come from the fact that SAUDs, by contrast to HDs, were under a detoxification program prohibiting alcohol consumption, and that this perceived unavailability prevented them from experiencing some craving (Papachristou et al., 2012a; Petit et al., 2017; Wertz and Sayette, 2001). Moreover, due to their knowledge of their inability to control drinking, they might have strategically withdrawn their attention from alcohol-related cues. Consistent with this idea, inpatients have been found to show an avoidance for alcohol-related visual stimuli, contrary to current drinkers who rather display an attentional bias (Field et al., 2004; Townshend and Duka, 2007). Finally, it remains possible that SAUDs, because of their patient status, were reluctant to admit experiencing craving. Therefore, future studies should consider including some physiological measures (e.g., heart variability or skin conductance response) to verify their lack of reactivity. Nonetheless, this result allows emphasizing that abstinent SAUDs under treatment represent a specific sample, clearly different from non-treatment seeking current drinkers, and that both populations are needed in studies tackling the question of alcohol craving.

Surprisingly, even when the alcohol-related exposure enhanced craving intensity in HDs, it did not seem to affect the strength of excitatory and inhibitory influences at play during action preparation. As such, contrary to our expectations, the level of preparatory changes in

MEPs probed following the VR immersion in a bar did not differ from what was observed in the neutral sections. The only evident change across the three sections was a strengthening of MEP suppression during the last block in controls, both in task-relevant and task-irrelevant muscles. Hence, consistent with a recent study performed in healthy participants (Vassiliadis et al., 2020), practicing the rolling ball task seems to strengthen MEP suppression, and this training-related change occurs in parallel with a speeding up of RTs. Intriguingly, this intensification of MEP suppression was less obvious in SAUDs, while it was totally absent in HDs. One potential explanation could lie in the resource depletion model, which assumes that trying to resist drinking depletes the cognitive resources available for other concurrent tasks requiring self-control (Muraven et al., 1998; Muraven and Shmueli, 2006). Thereby, the lack of strengthening during the last block might be an indirect consequence of prior alcohol-related exposure, with HDs and SAUDs not being able to beneficiate from training-related changes in MEP suppression following a confrontation to alcohol-related cues.

In any case, the impact of the alcohol-related exposure was weaker than expected, potentially because the urge to drink alcohol as elicited with the current procedure was not strong enough to have a significant effect on our measures. While VR technology is increasingly used to induce alcohol craving, it usually allows the viewer to interact within the virtual environment (Ghiţă and Gutiérrez-Maldonado, 2018). Here, we opted for videos displaying real-world contents, which improves the sense of realism but does not include any interaction. Hence, our results could have been different if we had used interactive scenes, even though the level of craving elicited by such immersion does not seem to be higher than the one reported in the present study (Simon et al., 2020). Alternatively, the fact that MEP changes were only assessed during the preparation of responses associated with neutral cues (rather than alcohol-related cues) could explain the lack of effect, such as suggested in prior works (Kreusch et al., 2017; Mainz et al., 2012).

In conclusion, by evaluating MEP changes in task-relevant and task-irrelevant muscles during action preparation, the current study indicates that a higher tendency to act characterizes both HDs and SAUDs, while a lack of inhibitory influences related to impulse control only concerns SAUDs. Hence, an abnormally high tendency to act would represent a common feature of hazardous drinking, leading individuals to excessive alcohol consumption. By contrast, deficient preparatory inhibition would manifest in more severe forms of AUD, potentially due to the neurotoxic consequences of chronic alcohol use. Nonetheless, we have to point out that our sample sizes were relatively small, limiting the generalizability of these findings. Hence, it would be interesting to confirm these outcomes on a larger group of individuals. Finally, while an exposure to an alcohol-related environment does not seem to alter these excitatory and inhibitory drives, future studies are needed to clarify this question. In particular, follow-up work should evaluate the impact of such exposure when the target response is directed towards alcohol-related, rather than neutral, cues.

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CRediT authorship contribution statement

Caroline Quoilin: Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original Draft, Writing – Review & Editing. Funding acquisition. **Philippe Timary:** . **Julie Duque:** Conceptualization, Writing – Review & Editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102738.

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