Neural bases of inhibitory control: Combining transcranial magnetic stimulation and magnetic resonance imaging in alcohol-use disorder patients

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Highlights:

- Neural source of motor preparatory suppression remains largely unknown.
- Extent of preparatory suppression was related to structural brain measures.
- Thinner medial prefrontal cortex was related to weaker preparatory suppression.
- Motor excitability appears as a valuable read-out of upstream cognitive processes.

Neural bases of inhibitory control: Combining transcranial magnetic stimulation and magnetic resonance imaging in alcohol-use disorder patients.

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Abstract

Inhibitory control underlies the ability to inhibit inappropriate responses and involves processes that suppress motor excitability. Such motor modulatory effect has been largely described during

action preparation but very little is known about the neural circuit responsible for its implementation. Here, we addressed this point by studying the degree to which the extent of preparatory suppression relates to brain morphometry. We investigated this relationship in patients suffering from severe alcohol use disorder (AUD) because this population displays an inconsistent level of preparatory suppression and major structural brain damage, making it a suitable sample to measure such link. To do so, 45 detoxified patients underwent a structural magnetic resonance imaging (MRI) and performed a transcranial magnetic stimulation (TMS) experiment, in which the degree of preparatory suppression was quantified. Besides, behavioral inhibition and trait impulsivity were evaluated in all participants. Overall, whole-brain analyses revealed that a weaker preparatory suppression was associated with a decrease in cortical thickness of a medial prefrontal cluster, encompassing parts of the anterior cingulate cortex and superior-frontal gyrus. In addition, a negative association was observed between the thickness of the supplementary area (SMA)/pre-SMA and behavioral inhibition abilities. Finally, we did not find any significant correlation between preparatory suppression, behavioral inhibition and trait impulsivity, indicating that they represent different facets of inhibitory control. Altogether, the current study provides important insight on the neural regions underlying preparatory suppression and allows highlighting that the excitability of the motor system represents a valuable read-out of upstream cognitive processes.

Keywords: alcohol use disorder; transcranial magnetic stimulation; motor system; inhibitory control; cortical thickness; neuroimaging.

1. Introduction

Appropriate human behavior entails the ability to perform goal-directed actions, a competence relying on the operation of distributed control processes that eventually leave their imprint on the motor system (Alamia et al., 2018; Derosiere and Duque, 2020; Lebon et al., 2018; Thura and Cisek, 2014). Such motor modulatory changes can be investigated non-invasively in humans by applying single-pulse transcranial magnetic stimulation (TMS) over the primary motor cortex (M1). When applied over M1, single-pulse TMS elicits motor-evoked potentials (MEPs) in targeted contralateral muscles, and the amplitude of these MEPs reflects the excitability of the corticospinal pathway at the time of stimulation (Bestmann and Duque, 2016; Hannah and Rothwell, 2017). Critically, a considerable amount of TMS studies has reported a drastic suppression in the activity of this motor output pathway during action preparation (Derosiere et al., 2020; Duque et al., 2017). In those studies, the task requires participants to choose between responding with the left or the right hand according to a preparatory cue, and to withhold their response until the onset of an imperative signal. When TMS pulses are applied between the cue and the imperative, MEPs probed both in a hand cued (i.e., selected) or non-cued (i.e., non-selected) for the forthcoming response display a much smaller amplitude relative to resting conditions (Grandjean et al., 2019; Greenhouse et al., 2015; Klein et al., 2016; Vassiliadis et al., 2018; but see Mars et al., 2007; van den Hurk et al., 2007), a phenomenon referred to as preparatory suppression (or inhibition).

Recently, we have reported a shortage of preparatory suppression in a clinical population of patients with severe alcohol use disorder (AUD) (Quoilin et al., 2018). These patients displayed a

much weaker suppression of MEPs during action preparation relative to matched healthy subjects. This between-group difference was mainly obvious in the left, non-dominant hand, i.e. in a condition where MEP suppression is normally the strongest. Indeed, the motor pathway controlling for the non-dominant limb is known to display more inhibitory influences than that controlling for the dominant one (Duque et al, 2007; Leocani et al., 2000; Wilhelm et al, 2016), an effect accounting for the fact that preparatory suppression is frequently assessed only in the left hand (Duque et al., 2016; Greenhouse et al., 2015; Labruna et al., 2019). Critically, the level of preparatory suppression was quite heterogeneous in AUD patients, with the extent of the shortage being related to the propensity to relapse in the subsequent year (Quoilin et al., 2018). Moreover, such as indicated by performance at the anti-saccade task and scores at the urgency subscale of the UPPS questionnaire, AUD patients displayed poorer response inhibition abilities and higher trait impulsivity than controls (Quoilin et al., 2018), in line with the well-known relationship between AUDs and deficient inhibitory control (Dick et al., 2010). Importantly, the fact that a lack of preparatory suppression was unveiled in a population characterized by deficient inhibitory control reinforces other evidence in favor of one of the most predominant idea regarding the functional role of such motor suppression (Burle et al., 2016; Klein et al., 2014; Meckler et al., 2011; Quoilin et al., 2019). According to this view, preparatory suppression of the motor pathway would support behavioral inhibition, thus helping to avoid the emergence of premature or inappropriate motor responses and, more generally, to ensure some sort of impulse control (Duque et al., 2017). In other words, by underlying the ability to suppress and to hold back inappropriate responses, motor suppression during action preparation would contribute to inhibitory control (Derosiere et al., 2018; Klein et al., 2014).

While past research has provided an extensive description of various aspects of preparatory suppression, very little is known about the neural structures responsible for its implementation. Potential candidates are the pre-supplementary area (pre-SMA), the lateral prefrontal cortex, and the dorsal premotor cortex, but this assumption is based only on two studies using repetitive TMS to assess the specific contribution of a priori defined cortical regions of interest (Duque et al., 2012, 2013). In fact, most knowledge on the neural substrates of inhibitory control derives from observations made in the stop signal task, where subjects have to cancel an already initiated response following the presentation of a stop signal (Aron, 2007; Bari and Robbins, 2013; Chambers et al., 2009; Derosiere and Duque, 2020; Logan, 1994; Verbruggen et al., 2019). This work has allowed highlighting a network encompassing medial and lateral prefrontal regions, including the pre-SMA and the right inferior frontal cortex, as well as subcortical structures, such as the basal ganglia and the cerebellum (Aron et al., 2016; Bari and Robbins, 2013; Clark et al., 2020; Ji et al., 2019). Yet, stopping an ongoing action in response to an external cue represents only one specific aspect of inhibitory control, while appropriate control often relies on the ability to prepare the right action and to withhold premature or inappropriate ones, a competence that may recruit different brain mechanisms (Derosiere and Duque, 2020; Raud et al., 2020; Swick et al. 2011). Hence, preparatory suppression seems to embody a more comprehensive measure of inhibitory control but evidence regarding its neural sources is scarce.

Critically, AUD patients have structural damage across the brain, mostly due to the considerable neurotoxic effects of chronic alcohol consumption (Fein et al., 2002; Grodin and Momenan, 2017; Roland et al., 2018; but see Wiers et al., 2015). Compared to healthy controls, they display volumetric loss and decreased cortical thickness, manifest by an overall ventricular enlargement as well as a grey matter reduction, notably in the frontal, parietal, and temporal lobes, the insula,

the thalamus, and the cerebellum (Chanraud et al., 2007; Momenan et al., 2012; Rolland et al., 2018). While brain atrophy is widespread, the most pronounced damages are found in frontal regions (Chanraud et al. 2007; Durazzo et al., 2011; Fortier et al., 2011; Xao et al., 2015), with the extent of grey matter loss being related to impaired executive functioning (Chanraud et al. 2007). Finally, an altered activation has been reported among prefrontal areas and basal ganglia during behavioral inhibition (Czapla et al., 2017; Hu et al., 2015; Li et al., 2009; Sjoerds et al., 2014). Altogether, this literature seems to indicate that AUD patients represent an appropriate population to investigate relationships between structural brain damage and deficient inhibitory control.

The present study aimed at better understanding the neural circuit underlying preparatory suppression, by assessing the link between this motor phenomenon and brain morphometry in a sample of severe AUD patients. To do so, all participants underwent a structural magnetic resonance imaging (MRI) and performed a TMS experiment, where the degree of preparatory suppression was quantified based on the strength of MEP suppression during action preparation in the left non-dominant hand. A whole-brain approach was employed to explore associations between this neural measure and cortical thickness. In addition, correlations with volumes of specific subcortical structures were evaluated. Finally, we examined behavioral inhibition and trait impulsivity, using performance at the anti-saccade task and scores at the urgency subscale of the UPPS questionnaire, respectively (Quoilin et al., 2018). We expected to observe negative associations for regions contributing to inhibitory control.

2. **Materials and Methods**

2.1. Participants

Forty-five subjects with severe AUD (19 women), diagnosed by a psychiatrist according to DSM-5 criteria, were recruited during the third week of their alcohol detoxification program (St. Luc Academic Hospital, Université catholique de Louvain, Brussels, Belgium). They were all right-handed, such as determined with a shortened version of the Edinburg Handedness Inventory (Oldfield, 1971). Moreover, all patients were free of any other psychiatric or substance use disorder (except nicotine dependence), but also of medical or neurological disorder and drug treatment that could influence brain morphometry, performance or neural activity, including any benzodiazepine. The mean alcohol consumption before detoxification was 19.3 alcohol units (standard deviation (SD) = 10.82) per day (an alcohol unit = 10 grams of pure ethanol), and the mean duration of AUD was 12.3 years (SD = 9.61). All patients were tested between day 16 and day 20 of abstinence and were no longer on withdrawal medication. They all gave written informed consent, following a protocol approved by the Biomedical Ethic Committee of the Saint-Luc University Hospital, Université catholique de Louvain.

2.2. Clinical assessment and measures of inhibitory control.

2.2.1. Psychopathological 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 et al., 1983) and the 13-item short form of the Beck Depression Inventory (BDI; Beck, 1961; Collet and Cottraux, 1986).

2.2.2. Neural measure. Preparatory suppression was evaluated by applying single-pulse TMS over the right M1 when participants were performing an instructed-delay choice RT task implemented with Matlab 7.5 (Mathworks, Natick, Massachusetts, USA) using the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997). This task, called the "rolling ball" task (Figure 1A and B), has been used in several past studies, producing a consistent preparatory suppression in healthy individuals (Grandjean et al., 2019; Quoilin et al., 2016, 2018; Vassiliadis et al., 2018). Basically, participants are required to choose between responding with a left or a right index finger abduction according to the position of a preparatory cue that appears on a computer screen placed in front of them (i.e., a left or right-side ball separated from a goal by a gap), and to provide their response as fast as possible after the onset of an imperative signal (i.e. a bridge connecting the ball and the goal). Once a correct response is detected, the ball rolls over the bridge to reach the goal. Importantly, responses provided before the onset of the imperative cause the ball to fall into the gap. Between the trials, participants are asked to stay still with forearms resting in a semi-flexed position and hands placed palms down on the response device.

The sequence of events of a typical trial is shown on Figure 1A. Each trial started with the presentation of a blank screen for 1000 ms. Then, the preparatory cue was displayed, allowing participants to prepare their movement. After a random period of 1000-1200 ms, the imperative signal appeared and remained visible until a finger response was detected (700 ms max). Finally, a feedback score reflecting the performance appeared for 500 ms: correct responses led to positive scores (inversely proportional to the RT, ceiling at + 25), while errors resulted in a fixed negative score (- 15). The inter-trial interval was set at 2300 ms.

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FIGURE 1 NEAR HERE
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The testing always began with a short practice block to allow participants to become familiar with the task and to learn to stay relaxed between each response. Then, each subject performed 2 experimental blocks of 56 trials, with one TMS pulse applied over the right M1 on each trial. Single TMS pulses were generated with a figure-of-eight coil (wing external diameter, 70 mm) connected to a Magstim 200 magnetic stimulator (Magstim, Whitland, Dyfed, UK). The coil was placed tangentially on the scalp, with the handle pointing backwards and laterally at 45° angle away from the midline, approximately perpendicular to the central sulcus. Prior to the task, the optimal coil position for eliciting MEPs in the contralateral left first dorsal interosseous (FDI) was identified and marked on a head cap placed on the participant's scalp to provide a reference mark throughout the experiment (Vandermeeren et al., 2009). The resting motor threshold (rMT) was determined as the minimal TMS intensity required to evoke MEPs of about 50 μV peak-to-peak in the relaxed FDI muscle in 5 out of 10 consecutive stimulations. Across participants, the rMT corresponded to 47.2 (SD = 9. 24) % of the maximum stimulator output (MSO).

During the rolling ball task, the intensity of TMS was set at 115 % of the rMT. On each trial, the TMS pulse was delivered at one of 2 possible timings (Figure 1B). To establish a baseline measure of corticospinal excitability (CSE), the TMS pulse occurred at the onset of the blank screen, eliciting MEPs at rest (BASELINE; 18 MEPs/block). In other trials, to assess preparatory suppression, TMS was delivered 950 ms after the onset of the preparatory cue, when subjects were withholding their prepared response (PREPARATION; 38 MEPs/block). At the latter

timing, MEPs could either occur when the targeted FDI was selected (i.e., left response trials; 19 MEPs/block) or non-selected (i.e., right response trials; 19 MEPs/block) for the forthcoming response. The order of trials at BASELINE and at PREPARATION in a selected and a non-selected hand was randomized within each block. Importantly, PREPARATION MEPs probed in a selected or non-selected setting were expressed in percentage of MEPs probed at BASELINE; a value below one hundred reflects preparatory suppression.

Electromyography (EMG) was recorded from surface electrodes (Neuroline, Medicotest, Oelstykke, Denmark) placed over the left FDI muscle. EMG data were collected for 3200 ms on each trial, starting 200 ms before the TMS pulse. The raw EMG signals were amplified (gain, 1K) and digitized at 2000 Hz for off-line analysis. The latter consisted in extracting the peak-to-peak amplitude of MEPs recorded in the left FDI. In order to prevent contamination of MEP measurements by significant fluctuations in background EMG, trials with any background activity larger than 30 μV in the 200 ms window preceding the TMS pulse were excluded from the analysis (Quoilin et al., 2019). As such, the EMG root mean squares for trials included in the analyses averaged 14.2 μV (SD = 10.4). Trials in which subjects made an error were also removed from the data set. The remaining MEPs were classified according to the experimental condition within which they had been 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 23.0 (i.e., 63.9 % of the trials), 23.5 (i.e., 61.8 % of the trials), and 23.9 (i.e., 63.1 % of the trials) trials remained to assess CSE at BASELINE and at PREPARATION in a selected or non-selected setting, respectively.

2.2.3. Behavioral measure. The anti-saccade task (adapted from Roberts et al., 1994) was used to assess response inhibition. Following the experimental procedure recommended by Miyake et al. (2000), participants successively performed two control blocks (parts A and B) and an experimental block (part C), which were identical in their structure and requirements except that parts A and B did not involve executive functions while part C did. As shown on Figure 1C, each trial started with the presentation of a fixation cross in the middle of the screen for 1500 to 3500 ms, followed by the onset of a target stimulus. This stimulus was an arrow displayed for 150 ms on the left or the right side of the screen, before being masked by a gray cross-hatching square. The participant's task was to indicate the orientation of the arrow (towards the left, the right or upwards) by pressing the corresponding key on a keyboard with the right hand (with the index, the middle, or the ring finger, respectively). In the non-executive block A (40 trials, no cue condition), the sequence of events for each trial occurred as describe above. In the non-executive block B (40 trials, congruent condition), a visual cue was presented for 225 ms between the fixation cross and the target stimulus on the same side of the arrow. Finally, the executive block C (80 trials, incongruent condition) involved trials in which the visual cue was systematically displayed on the side opposite to the target stimulus, and thus requiring participants to inhibit the automatic saccadic eye movement towards the cue to be able to correctly identify the orientation of the arrow. This design enabled to calculate the so-called anti-saccade cost, which was based on the extraction of the specific executive subcomponent while controlling for visual and motor involvements. Accordingly, this measure was computed by calculating the difference between the average scores obtained in the executive block C and the average scores recorded in the non-executive blocks A and B, for both reaction times (RTs, in ms) and accuracy (in percentage of correct responses).

2.2.4. Trait measure. Trait impulsivity was evaluated using 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 (Van der Linden et al., 2006; Whiteside et al., 2005).

2.3. MR data acquisition and processing.

Images were acquired on a 3T MRI scanner (Achieva, Philips Healthcare, Eindhoven, The Netherlands) with a 32-channel phased array head coil. For each participant, detailed anatomy of the whole brain was provided by a three-dimensional T1-weighted gradient sequence with an inversion prepulse (Turbo Field Echo) acquired in the sagittal plane using the following parameters: time of repetition (TR) = 9.1 ms, time of echo (TE) = 4.6 ms, flip angle (FA) = 8°, field of view (FOV) = 220 x 197 mm^2, acquisition matrix = 296 x 247 (reconstruction 320 x 320), in-plane resolution = 0.81 x 0.95 mm^2 (acquisition) reconstructed in 0.75 x 0.75 mm^2, 150 slices, slice-thickness = 1 mm, SENSE factor = 1.5 (parallel imaging).

Cortical reconstruction and volumetric segmentation were performed using the FreeSurfer image analysis pipeline (version 5.1; available at http://surfer.nmr.harvard.edu). The final segmentation is based on both a subject-independent probabilistic atlas and subject-specific measured values. The atlas is built from a training set of 40 participants whose brains were labeled by hand (Dale 1999; Fischl et al. 2002, 2004). After completion of the pipeline, each segmentation was visually inspected and corrected when necessary. Only small skull strips errors were found and corrected before running the data through the pipeline again. Overall, the pipeline allowed the automatic generation of cerebral volumetric measures (in mm^3) and the production of a surface 3D model of

cortical thickness, the latter being calculated as the shortest distance between the grey matter/white mater boundary and pial surface at each vertex across the cortical mantle (in mm).

2.4. Statistical analyses.

First, we carried out descriptive statistics (mean ± SD) to characterize our sample of AUD patients. Then, to assess their level of inhibitory control, one-sample t-tests were performed on neural, behavioral and trait measures: preparatory suppression in the selected and non-selected setting (i.e. PREPARATION MEPs expressed in percentage of BASELINE MEPs) was compared to a constant value of 100, the anti-saccade cost (both in terms of RTs and accuracy) to a constant value of 0 (i.e., absence of cost), and scores reported at the four subscales of the UPPS questionnaire were compared to normative values obtained in a large sample of healthy subjects (Van der Linden et al. 2006). For each measure of inhibitory control, Bonferroni corrections were applied to control for multiple comparisons. Finally, we assessed the presence of a potential link between the different measures of inhibition with partial Pearson's correlations, when controlling for age, and with a Bonferroni correction for multiple comparisons.

Second, we investigated potential relationships between brain morphometry and our variables of interest (i.e. preparatory suppression, anti-saccade cost, and scores at the urgency subscale).

In order to examine whole-brain relationships between cortical thickness and inhibitory control, a vertex-wise general linear model (GLM) was run using the FreeSurfer Qdec tool after smoothing cortical maps at full width half-maximum (FWHM) of 10 mm. As such, we used a GLM model to test the association between cortical thickness at each vertex with scores on each variable of

interest, while including the factor AGE as the nuisance factor. In order to avoid clusters appearing significant by chance (i.e. false positives), all results were corrected for multiple comparisons using a Monte Carlo Null-Z Simulation with 5000 iterations ($p < 0.05$).

Associations between subcortical structures and inhibitory control were also evaluated. First, measures of total subcortical gray matter volume were extracted from the individual MRIs. Volumetric measures of grey matter were also obtained for several basal ganglia (caudate nucleus, putamen, and globus pallidus), thalamus, and cerebellum. Partial Pearson's correlations between measures of subcortical volumes and inhibitory control were then performed, controlling for age and intracranial volume and with a Bonferroni correction for multiple comparisons.

With the exception of assessments involving the cortical thickness, analyses were carried out using Statistica 10 (StatSoft, Cracow, Poland). The statistical significance was set at $p < 0.05$.

3. Results.

3.1. Sample characteristics.

The characteristics of our sample are provided in Table 1. Overall, based on the cut-off scores previously established and validated (Beck and Beck, 1972; Knight et al., 1983; Spielberg et al., 1983), AUD patients did not display significant clinical symptoms of state anxiety. By contrast, they displayed moderate symptoms of trait anxiety and suffered from mild to moderate depression.

Interestingly, AUD patients did not show any significant preparatory suppression, regardless of whether it was probed in a selected (t_{42} = -1.38; p = 0.17, i.e. > 0.05/2) or non-selected setting (t_{42} = -1.86; p = 0.07, i.e. > 0.05/2), corroborating our prior observation that these patients suffer from a lack of motor inhibition during action preparation (Quoilin et al., 2018). Moreover, the anti-saccade cost was significant, both in terms of RTs (t_{44} = 2.99; p < 0.01, i.e. < 0.05/2) and accuracy (t_{44} = 7.43; p < 0.001, i.e. < 0.05/2). Finally, regarding trait impulsivity, AUD patients presented particularly high levels of urgency (t_{44} = 3.73; p < 0.001, i.e. < 0.05/4; by comparison to a constant value of 28.75 such as reported in Van der Linden et al., 2006); scores on the other subscales of the UPPS questionnaire were in the normal range (all $|t|_{44}$ > -2.00 and p > 0.05/4). Notably, we did not find any significant correlation between these different measures (all -0.10 < r < 0.28 and p > 0.06, i.e. > 0.05/28), suggesting that they reflect different facets of inhibitory control.

Table 1. Characteristics of the alcohol use disorder (AUD) group [Mean *(SD)*].

	AUD (n = 45)[1]
Demographic and psychopathological measures	
Age	50.2 *(9.67)*
Gender (n women)	19
Education level[2]	14.1 *(2.33)*
Tobacco (n smokers)	22
State anxiety	35.8 *(12.04)*
Trait anxiety	49.8 *(10.55)*
BDI	8.7 *(6.37)*
Measures of inhibitory control	
Neural measure: Preparatory suppression	
Selected setting	91.3 (41.13)
Non-selected setting	89.0 (38.88)
Behavioral measure: Anti-saccade cost	
RT (ms)	38.8 *(86.81)*
Accuracy (% correct)	18.2 *(16.41)*
Trait measure: UPPS scale	
Urgency	32.8 *(7.28)*
Lack of premeditation	21.4 *(5.20)*
Lack of perseverance	19.4 *(4.59)*
Sensation seeking	29.2 *(8.04)*

[1]Except for the measures of preparatory suppression, which included only 43 subjects. [2]The education level reflects the number of years of education completed since starting primary school.

3.2. Vertex-wise whole-brain analyses of cortical thickness.

As displayed in Table 2 and Figure 2, the GLM analyses revealed negative relationships between cortical thickness and two of our measures of inhibitory control. First, the strength of preparatory suppression varied negatively with the thickness of a medial prefrontal cluster encompassing parts of the right superior-frontal gyrus and the right anterior cingulate cortex (ACC). Notably, this effect was only evident in a selected setting, but not when preparatory suppression was probed based on MEP in a non-selected setting. Hence, a weaker preparatory suppression (i.e. higher PREPARATION MEPs, expressed in percentage of BASELINE MEPs) in a hand that was selected for the forthcoming response was associated with a reduced cortical thickness is this area. Importantly, additional analyses demonstrated that this association was not driven by any change in background EMG activity. The other significant relationship was found for the anti-saccade cost (in terms of accuracy), which was negatively related to the thickness of a cluster in the right superior-frontal gyrus, corresponding to the SMA/pre-SMA; the thinner the cortex in this region, the more AUD patients experienced a high cost.

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FIGURE 2 NEAR HERE

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Table 2. Significant relationship between cortical thickness and measures of inhibitory control in alcohol use disorder (AUD) patients.

Measures of inhibitory control	Anatomical region	Cluster size (mm^2)	X	Y	Z	*r*	*CWP*
Preparatory suppression (Selected setting)	Right anterior cingulate and right superior frontal	1108.4	13.8	22.4	30.5	-0.39	0.008
Anti-saccade cost (Accuracy)	Right superior frontal	916.2	22	16.7	50.8	-0.38	0.03

Coordinates are depicted as peak-coordinates within the Talairach space. Correction for multiple comparisons based on the Monte Carlo simulation method ($p < 0.05$), after adjustment for age. r = partial Pearson's correlation coefficient; *CWP* = cluster wise corrected p-value.

3.3. Volumetric analyses of subcortical structures.

Our analyses did not disclose any significant relationship between the volume of specific subcortical regions and our neural and trait measures of inhibitory control. By contrast, we observed some negative relationships for the behavioral measure: the stronger the anti-saccade cost was (i.e. the lower the accuracy), the smaller the total subcortical gray matter volume was ($r = -0.34$; $p = 0.025$), as well as the grey matter volume of the cerebellum ($r = -0.31$; $p = 0.041$ and $r = -0.36$; $p = 0.016$ for the left and right hemisphere, respectively). Nonetheless, these effects did not survive Bonferroni correction ($p = 0.0045$; i.e. 0.05/11).

4. Discussion

Preparatory suppression, defined as a drastic decrease in motor excitability during action preparation, is thought to support the ability to hold back premature or inappropriate responses and, more globally, to contribute to inhibitory control. Yet, while preparatory suppression has

been extensively described in the last decade, very little is known regarding the neural circuit responsible for its implementation. Here, we took advantage of the well-known structural brain damage and inhibitory control deficits characterizing AUD patients to identify candidate neural structures playing a role in motor preparatory suppression. This allowed highlighting a *medial prefrontal cluster*, encompassing parts of the right ACC and the right superior-frontal gyrus, whose thickness was associated with the strength of preparatory suppression. Besides, we also found a relationship between the cortical thickness of a *superior frontal cluster*, corresponding to the SMA/pre-SMA area, and a behavioral measure of response inhibition.

The main finding of the present study is that the strength of MEP suppression during action preparation was significantly associated with the cortical thickness of a medial prefrontal cluster. This cluster was centered on the rostral part of the right dorsal ACC, also frequently referred to as the anterior midcingulate cortex (Vogt, 2016), and spread over several surrounding regions. As such, it extended to parts of the perigenual ACC, to the cingulate sulcus, which encompasses the cingulate premotor areas, and to the dorsomedial prefrontal cortex, located on the superior-frontal gyrus. Interestingly, the dorsal ACC is one of the most broadly connected regions of the brain, connecting with frontal, parietal, and temporal regions, as well as with many subcortical structures (Loh et al., 2018; Touroutoglou et al., 2020; Vogt, 2016). Due to its position at the intersection of multiple brain networks, it represents a major hub of communication, which explains its demonstrated contribution to various cognitive processes, such as conflict resolution, error detection, reinforcement learning, motor control, decision-making, or response selection (Bari and Robbins, 2013; Touroutoglou et al., 2020; Vogt, 2016). In particular, the cingulate premotor areas show reciprocal connections with the prefrontal, the primary motor and the premotor cortices, as well as direct projections to the spinal cord (Loh et al., 2018). Hence, the

cluster reported here encompasses areas ideally placed to integrate information coming from widespread regions in order to drive goal-directed behavior or, in other words, to appropriately modulate the activity within the motor system.

The fact that muscle potentials were abnormal in AUD patients may appear at odds with the predominant cognitive dimension of the disorder. Yet, it is less surprising when remembering that the amplitude of MEPs reflects the summation of multiple excitatory and inhibitory inputs shaping the level of excitability of the corticospinal pathway at the time of stimulation (Derosiere and Duque, 2020). Those inputs can originate from the stimulated primary motor cortex itself, but also from other cortical or subcortical regions (Bestmann and Krakauer, 2015; Derosiere et al., 2020; Duque et al., 2017). Hence, although MEPs are often taken as physiological markers of processes operating at the level of movement control, their amplitude also reflects other dimensions of motor behavior, some of which rely on upstream cognitive processes. Our findings further demonstrates that the motor system output can serve as a valuable read-out of control processes, in line with an integrative view of action control (Cisek and Kalaska, 2010), in which circuits distributed across the brain are able to guide behavior throughout inputs sent to the motor system.

The strength of preparatory suppression was not fully related to the identified cluster, as the association only concerned MEPs probed in a hand selected for the forthcoming response, whereas we did not find a significant relationship between cortical thickness and MEPs probed in the non-selected setting. Consistent with this finding, a growing body of evidence indicates that preparatory suppression does not result from a unitary process but rather reflects the joint impact of several overlapping inputs, some of which being more specifically responsible for the effect observed in the selected setting (Derosiere and Duque, 2020; Duque et al., 2017). These more

selective inputs appear to have spinal relays, as evident from a reduction of Hoffman-reflexes (i.e., a measure of spinal excitability) observed only when probed in a selected setting (Duque et al., 2010; Hasbroucq et al., 1999). Moreover, they have already been related to the premotor cortex. As such, a virtual lesion of this area during action preparation weakens the MEP suppression in the selected hand, but has no impact on MEPs probed in the non-selected one (Duque et al., 2012). The premotor cortex is known to send direct projections to spinal interneurons and may thus promote the subcortical aspect of preparatory suppression. In view of the current results, it seems that the cingulate cortex, and more particularly the cingulate premotor areas, may also contribute to this selective motor suppression.

The second cluster identified here was located on a section of the right superior-frontal gyrus, which corresponds to the SMA/pre-SMA area. A reduced cortical thickness of this region was associated with a poorer performance at the anti-saccade task, consistent with the recognized participation of both sub-regions in motor control, even if they serve different roles (Ruan et al., 2018). While the SMA contributes to motor planning, the pre-SMA appears as a control area updating motor plans and guiding movement selection, notably by resolving the competition between action contingencies under situations of conflict (Duque et al., 2013; Ruan et al., 2018; Taylor et al., 2007). A large compilation of lesion, TMS, and neuroimaging studies have demonstrated the significant role of SMA/pre-SMA area in response inhibition (Chen et al., 2009; Floden and Stuss, 2006; Picton et al., 2007; Swick et al., 2012; Watanabe et al., 2015). Interestingly, at the intersection of those two regions stands the supplementary eye field (SEF), which belongs to the oculomotor system. Because the SEF has been consistently identified in neuroimaging studies contrasting neural activities during anti- and pro-saccade trials (Cieslik et al., 2016; Jamadar et al., 2013), and because its degree of activation is related to saccadic

performance (Grosbras et al., 1999; Jamadar et al., 2015), the SEF is thought to allow biasing the oculomotor system in favor of a controlled anti-saccade movement over prepotent pro-saccade responses (Schlag-Rey et al., 1997).

Performance at the anti-saccade task also showed some association with subcortical measures, and especially with the grey matter volume of the cerebellum. While these findings have to be interpreted with caution as they did not survive the Bonferroni correction, they deserve discussion. As such, they allow reminding us the too often forgotten contribution of this subcortical structure to executive functioning. Traditionally, the cerebellum was perceived as exclusively involved in movement execution and motor coordination and was frequently neglected in neuroimaging studies, probably due to a cortico-centric bias (Clark et al., 2020; Moulton et al., 2014). Yet, it is now clear that this structure participates in a range of cognitive functions, including response inhibition (Stoodley and Schmahmann, 2010). Accordingly, patients with cerebellar damage display impaired inhibitory abilities (Brunamonti et al., 2014; Tanaka et al., 2003), while clinical populations characterized by a lack of inhibitory control, including AUD patients, also often show cerebellar dysfunction (Moulton et al., 2014; Segobin et al., 2014). Furthermore, and in agreement with the current results, cerebellar activity in healthy subjects has been related to inhibitory control performance (Ghahremani et al., 2012; Jimura et al., 2014).

In contrast to the neural and behavioral measures of inhibitory control, we did not find any significant association between trait measures (i.e. scores at the urgency UPPS subscale) and brain morphometry. The lack of relationship between these variables was not surprising for several reasons. First, while many studies performed in healthy participants have reported a

negative correlation between scores at questionnaires of impulsivity and morphometric measures (Guerrero-Apolo et al., 2018; Matsuo et al., 2009; Nostro et al., 2016; Schilling et al., 2012; Wang et al., 2017), the replicability of those associations in healthy populations is now seriously called into question (Boekel et al., 2015; Genon et al., 2017, Masouleh et al., 2020). Second, trait impulsivity refers to a stable characteristic, whereas brain damage represents gradual consequences of chronic alcohol consumption. Interestingly, structural brain alterations pre-exist in young adolescents who are genetically at higher risk of developing AUD disorders (Benegal et al., 2007; Henderson et al., 2018). Moreover, a negative correlation between trait impulsivity and grey matter volume has been found in alcohol abusers having only a short alcohol use history (Asensio et al., 2016). Hence, it might be that brain abnormalities relating to certain personality traits, such as impulsivity, were present before alcohol consumption, predisposing individuals to AUDs, but that the association was masked by the chronic effects of alcohol, explaining the lack of correlation here.

Altogether, we identified two cortical clusters, showing a relationship with preparatory suppression or performance at the anti-saccade task, respectively. Interestingly, both clusters were located in the frontal cortex of the right hemisphere. This lateralization could reflect a right-hemispheric dominance for inhibitory control (Aron et al., 2014; Li et al., 2009). Alternatively, and as supported by studies showing an enhanced sensitivity of the right hemisphere to the neurotoxic effects of alcohol (Demirakca et al., 2011; Mechtcheriakov et al., 2006; Momenam et al., 2012), structural brain damage could have been more pronounced in the right hemisphere, increasing the likelihood to disclose a correlation on that side. In addition, there was no overlap between both clusters, suggesting that preparatory suppression and response inhibition might rely on different brain networks. In line with this hypothesis, we did not find any significant

association between the strength of MEP suppression and the anti-saccade cost, corroborating prior observations in a smaller sample (Quoilin et al., 2018). Besides, those variables did not significantly correlate with scores at the UPPS urgency subscale, which indicates that neural, behavioral and trait measures represent different facets of inhibitory control.

In summary, by considering brain morphometry in severe AUD patients, the current study provides important insight into the neural circuitry underlying preparatory suppression, highlighting a cluster in the medial frontal region centered on the cingulate cortex. Our results also draw attention on the fact that inhibitory control is not a unitary process, stressing the importance to use different approaches to address it. More generally, the current findings support the view that excitability of the motor output pathway, probed based on MEP amplitudes, represents a valuable read-out of modulatory changes generated by upstream cognitive processes.

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Declaration of competing interest.

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Data and code availability statement.

The processes data are available on Mendeley Data (Dataset: Quoilin, Caroline (2020), "Neural bases of inhibitory control", Mendeley Data, v2; http://dx.doi.org/10.17632/wsv95z4xcr.2).

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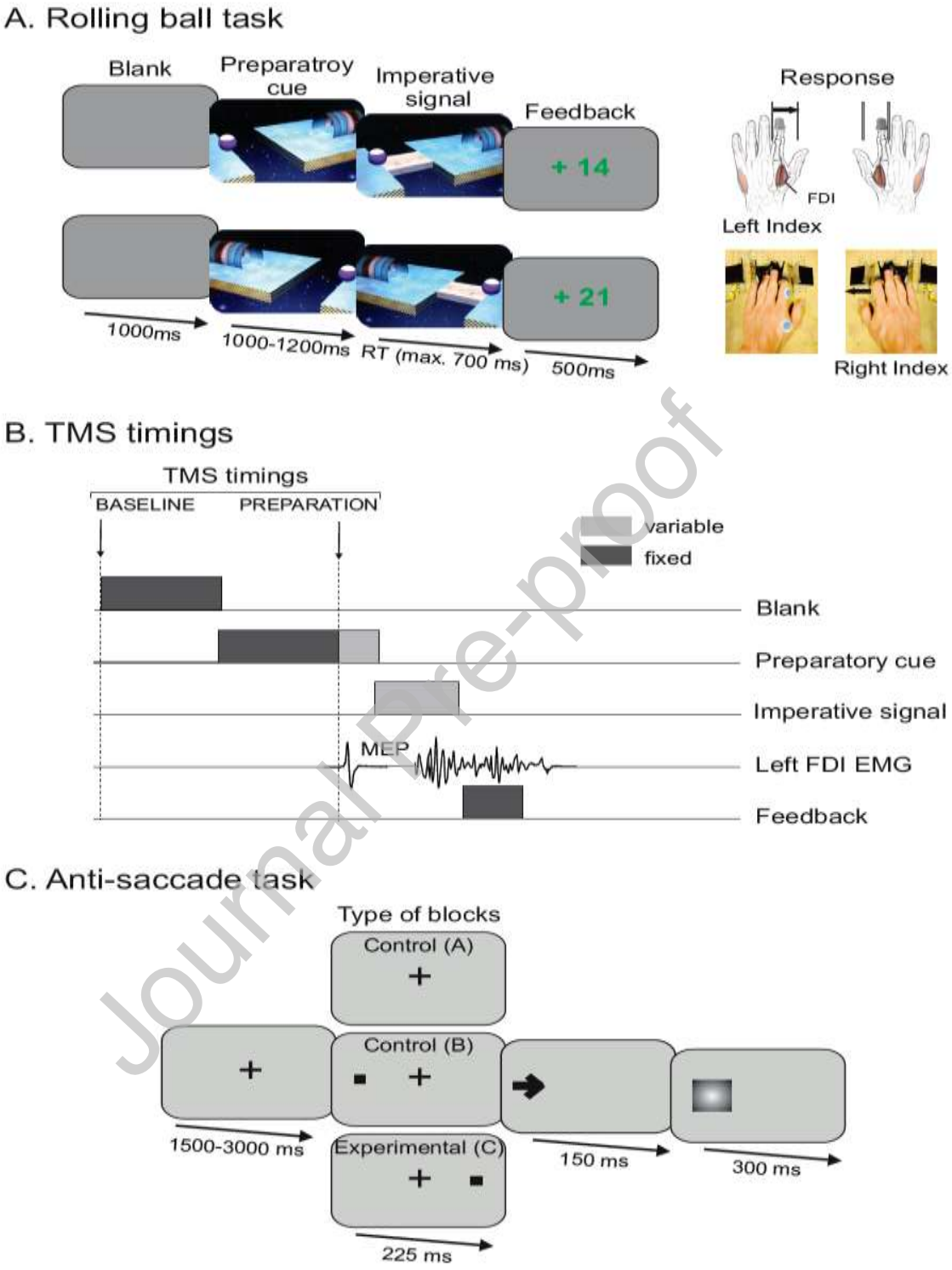

Figure 1. Experimental procedures to measure preparatory suppression (A and B) and behavioral inhibition (C). **(A)** Rolling ball task. Subjects performed an instructed-delay choice reaction time

task, requiring them to choose between an abduction movement of the left (upper trace) or right (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). Each trial started with the presentation of a blank screen for 1000 ms. Then, the preparatory cue was displayed (random duration; 1000 – 1200 ms) and was followed by the imperative signal, which remained visible until the subject responded (700 ms max). Finally, a feedback score reflecting how fast and accurate subjects had been was displayed for 500 ms. 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)** TMS timings. One single TMS pulse was delivered in each trial over the right primary motor cortex (M1) at two possible timings: either at the onset of the blank screen (BASELINE), or 950 ms after the onset of the preparatory cue (PREPARATION). FDI = first dorsal interosseous; TMS = transcranial magnetic stimulation; MEP = motor-evoked potential. **(C)** Anti-saccade task. Following the experimental procedure recommended by Miyake et al. (2000), participants successively performed three different blocks, in which they had to indicate the direction of an arrow (towards the left, the right, or upwards) by pushing a button with the right hand (with the index, the middle, or the ring finger, respectively). The arrow was presented very briefly (i.e. 150 ms) on the left or the right side of the screen before being masked by a gray cross-hatching square. The A and B blocks consisted in control blocks, while the block C represented the experimental block, in which participants had to inhibit an automatic saccadic eye movement towards a visual disturbing cue in order to correctly process the arrow. By contrasting performance in the experimental and control blocks, this design allowed to obtain the anti-saccade cost, both in terms of reaction times (RTs) and accuracy (percentage of correct responses).

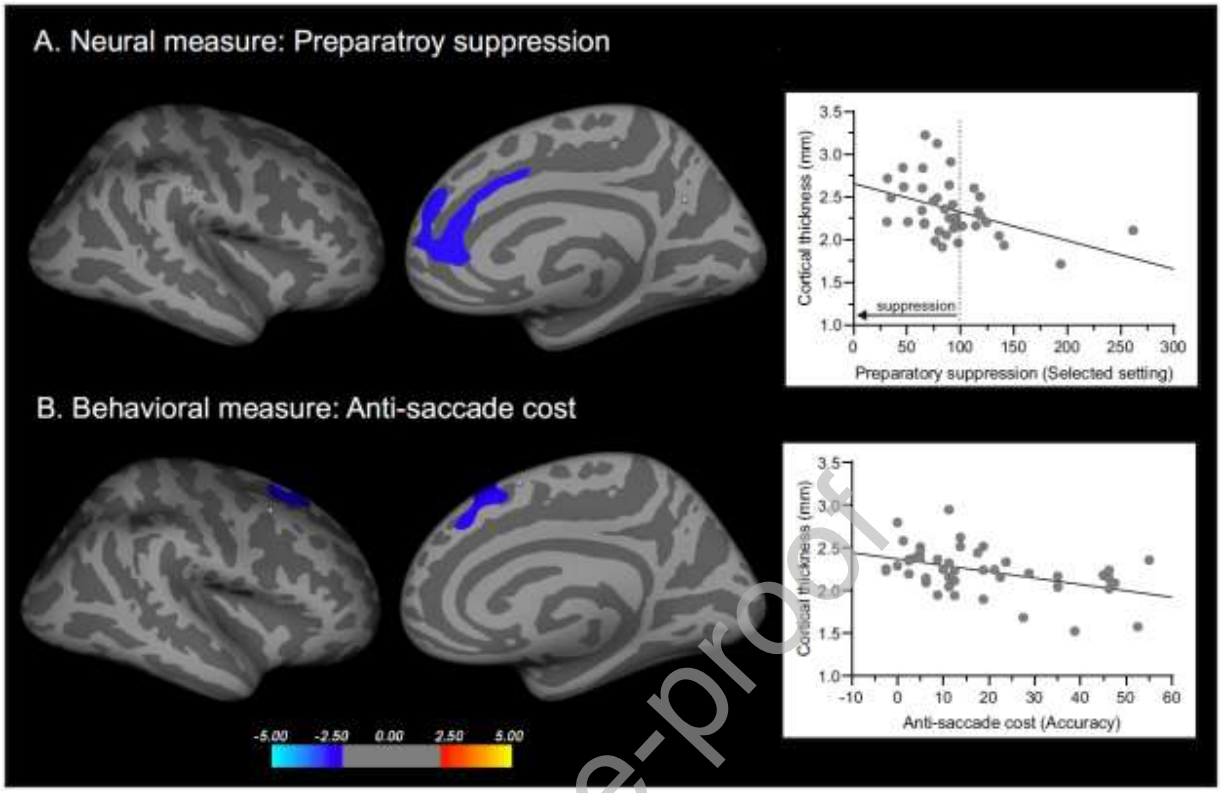

Figure 2. Significant relationships between cortical thickness and measures of inhibitory control. On the left, cortical maps show the brain areas in which cortical thickness was found to be negatively associated with (A) the strength of preparatory suppression (probed when the hand was selected for the forthcoming response) and (B) the anti-saccade cost (in terms of accuracy). Those clusters were significant after multiple comparison correction using Monte Carlo simulation ($p < 0.05$) and adjustment for age. On the right, the corresponding scatter plots are displayed. Please note the two extreme values regarding preparatory suppression, with two participants showing a considerable facilitation during action preparation. Importantly, the significant negative relationship displayed on the scatter plot remains when those two participants are excluded.