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Semantic inhibition impairment in college students with depressive states as evidenced by EEG and pupillometry during the hayling task

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In this study we tested whether depression is associated with impaired semantic inhibition, resulting in symptoms of rumination and anhedonia. For this purpose and using the Beck Depression Inventory II (BDI-II) college students with depressive states (DEP) and matched controls (CTL) performed a Hayling's task, while EEG and pupillometry measures were recorded. Participants were asked to complete sentential contexts with either a highly associated word (initiation) or a non-related word (inhibition), in response to randomly presented trial-by-trial cues. The DEP group, compared to the CTL group, showed lower performance, and reduced frontal negativity (N450) in inhibition trials. Source analyses revealed greater activation for inhibition trials than for initiation trials in bilateral orbitofrontal cortex for the CTL group, but the difference was reduced and more left lateralized for the DEP group. In addition, the DEP group showed more pupil size reactivity to inhibition trials than the CTL group, indicating higher cognitive effort during semantic inhibition. Finally, self-reported rumination and anhedonia correlated with N450 in inhibition trials, and rumination correlated with pupil dilation. Overall, this research contributes to understanding the neural underpinnings of impaired semantic inhibition in individuals with depression, with potential clinical applications.

The prevalence of depression among college students is much higher than in the general population. According to a recent meta-analysis, about 30% of the students have some degree of depression[1]. This disabling state has been associated with deficits in executive control and inhibitory control functions. For example, behavioral studies revealed that individuals with depression have poor performance in inhibition-related tasks, such as the Go/NoGo[2,3], stop-signal[4], Stroop[5], or Hayling's tasks[6]. These tasks differ in their inhibitory demands. For instance, the Go/NoGo task and the stop-signal task involve motor inhibition, i.e., refraining from giving a prepotent response, as pressing a key. In contrast, the Stroop and the Hayling tasks require semantic inhibition, i.e., suppressing a word strongly associated with the context, while producing an alternative word. Specifically, in the Stroop task, participants have to name the ink color that in some cases mismatch the color referred by the word, and in the Hayling sentence completion task (herein HSCT), they are asked in some trials to suppress a highly associated word to complete a semantically restrictive context. In general, people with depression are slower and less accurate than controls in the task versions demanding inhibition (NoGo trials, Stop trials, incongruent Stroop, or inhibition trials in HSCT).

As mentioned above, one of the tasks that can assess semantic inhibition process is the HSCT, which is designed to measure the initiation (INIT) and the inhibition (INHIB) of verbal responses in linguistic contexts, by requiring participants to complete sentences with either a meaningful word or a word that does not fit the context, respectively. The contexts are so restrictive that most participants in the INIT condition complete the sentence with the same word (e.g., *Since it was raining in the street*, *I opened my…*). In contrast, the INHIB condition requires active suppression of the most obvious completion word and other related words to produce a totally unrelated word. The HSCT and the Stroop task are similar in that both involve conflict due to semantic

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interference. Also, both tasks share neural processes in the prefrontal cortex, including the anterior cingulate cortex (ACC), the dorsolateral (DLPFC), or the orbitofrontal (OFC) cortex which are brain regions associated with executive functions such as attention, inhibition, and cognitive control[7–10]. However, the two tasks differ in some important respects. The Stroop task primarily assesses selective attention and inhibitory control and has a strong perceptual component, necessary for naming the ink color. On the other hand, the HSCT appears to involve more complex processes related to language and cognitive control. The INIT trials require comprehension of the context, as well as word prediction and retrieval. In contrast, the INHIB trials involve inhibiting the initially activated completion word and searching for a new completion word that is semantically unrelated to the context. This process requires evaluating and successively retrieving and suppressing candidates until finding a suitable completion word that fits the specified criterion.

The HSCT has proven to be a useful tool in the study of neurological or mental health disorders that involve some degree of dysfunction in semantic inhibition processes. For example, this is the case in neurodegenerative disorders such as Alzheimer's disease[11,12] and Parkinson's disease[13], in schizophrenia[14,15], and in cognitive aging[16]. Most relevant here, the HSCT is appropriate to reveal semantic inhibition deficits in people with depressive states. Moreover, a meta-analysis study showed that persons with depression were slower to initiate responses and committed more errors than controls in the inhibition condition of HSCT[6].

In addition, studies with neuroimaging techniques in both controls and psychopathological participants have shown that the inhibition phase of the HSCT involves the activation of prefrontal areas (anterior cingulate cortex -ACC, dorsolateral prefrontal cortex -DLPFC) and parietal areas, related to executive control, as well as the temporal areas, related to semantic processing[17–19]. On the other hand, event-related potentials (ERPs) analyses have been widely employed to investigate the neural dynamics in depressed persons in inhibition-related tasks. For instance, studies with the Go/Nogo task showed that these patients have an altered modulation of P3 amplitude compared to controls in Nogo trials[10,20,21]. However, to our knowledge, no study recorded EEG during HSCT to explore the neural dynamics associated with semantic inhibition in depressive states, as we have done in the current research.

Pupillometry provides another valuable tool for examining cognitive processes during task performance. Pupil dilation is a continuous, sensitive, and reliable indicator of physiological arousal and neurocognitive processing, indexing the activity of the norepinephrine system in the brainstem's locus coeruleus[22]. It has been linked to cognitive load, attentional allocation, decision-making processes[23,24] and effort measurement in cognitive control tasks[25]. For instance, Rondeel et al.,[23] reported that the conditions demanding more cognitive control, such as incongruent Stroop trials, were associated with greater pupil dilation. In the context of the HSCT, pupil dilation may reflect increased cognitive effort or arousal during the response inhibition condition[25].

Some common symptoms associated with major depression but also with depressive states are rumination and anhedonia. Rumination consists of recurrent self-focused negative thoughts, frequently in the form of inner speech[26–28], without a progress towards a solution or resolution. It usually involves repetitively focusing on distressing thoughts, feelings, or problems, dwelling on them excessively, with self-criticism, worry, or replaying past events in one's mind. Rumination has been frequently associated with impairment in executive control and cognitive inhibition[29–33], and with a specific deficit in semantic inhibition processes in individuals with depression[6,34], as it involves difficulties to suppress recurrent thoughts. On the other hand, anhedonia is defined as a diminished ability to experience pleasure or a decreased interest or satisfaction in previously enjoyable activities, leading to a sense of apathy and emptiness. It has been attributed to impairments in the reward network (e.g., nucleus accumbens), but also in the cognitive control networks in the prefrontal cortex[35].

In the present investigation we employed for the first time a co-registration of EEG and pupillometry during HSCT performance, to explore how neurophysiological markers of semantic inhibition might differ in students with depressive states, compared to nondepressed individuals. The rationale is that individuals with depressive states show semantic inhibition impairment, which could be associated with the typical symptoms of rumination and anhedonia in depression they suffer. Most studies with the HSCT present the initiation and inhibition conditions separately in different blocks. However, this procedure has the potential problem that participants may use non-inhibitory strategies in the inhibition blocks, such as anticipating the response before hearing the sentence or not paying attention to the sentence[36,37]. To avoid this, we presented both types of trials in random order. On each trial, an incomplete sentence was presented auditorily, and the participant had to wait for a visual cue on the computer screen; a green cue indicated responding with the word congruent with the phase context (INIT condition), and a red cue indicated responding with a word outside the sentence context but maintaining gender and number agreement with the sentence context (INHIB condition).

Given the lack of EEG studies with HSCT with which to compare, we can rely on some similarity to other inhibition tasks. Thus, given the specific semantic character of inhibitory processes in the Hayling task, we might expect to find modulation of frontal N450, which is associated with semantic conflict in the Stroop task[7–10]. That is, we hypothesize that INHIB trials, compared to INIT trials, will increase the N450 component as a signal of conflict and semantic inhibition. Another possibility is to also find some modulation of general ERP markers of conflict or inhibition similar to those found in NoGo trials in the GO/NOGO paradigm[20,21,30]. That is, potentiation of N2 and/or P3, corresponding to selective attention and inhibitory control, respectively[38]. As for pupillometric measures we may expect greater pupillary dilation in the response inhibition condition than in the response initiation condition of the HSCT, reflecting greater cognitive effort and arousal in the suppression of prepotent semantic responses.

The most important hypotheses, however, concern differences between participants with depression (DEP) and nondepressed controls (CTL), who were selected from a large sample of college students according to their scores on the Beck Depression Inventory (BDI-II)[39]. This is not a diagnostic tool per se, although it is widely used as an indicator of severity of individuals' depression states in the past few weeks. Concerning the ERP measures, we expect the DEP group, compared to the CTL group, to show reduced neural activity on inhibition trials, due

to their hypothesized impairment of semantic inhibition functions. Specifically, the N450 component, which can index semantic inhibition in INHIB trials, would be reduced in DEP participants. Furthermore, given that some studies have reported functional asymmetry in the brain hemispheres (right hemisphere hyperactivation and/or left hemisphere hypoactivation) in people with severe depression[40–46], we expect that the N450 also shows hemispheric asymmetry in the DEP group associated with semantic inhibition in the HSCT, reflecting the deficit in cognitive control required to manage conflict stimuli in depression.

With respect to pupillary reactivity, we predict that pupil dilation on INHIB trials would be larger in DEP participants than in CTL participants, indicating greater cognitive effort and/or hyperactivity of the norepinephrine system during semantic inhibition. On the other hand, we will explore correlations between self-report measures (rumination, anhedonia) and neurophysiological measures (ERPs and pupil dilation). We expect significant correlations between the neurophysiological response to INHIB trials (e.g., N450, and/or pupil dilation) and rumination and anhedonia. Finding these correlations could be evidence of association between neurophysiological and self-report measures, although causal interpretations could not be established. Finally, both pupil dilation and N450 may be sensitive to inhibitory demands in the HSCT, although they would index different functions and neural systems. That is, pupil reactivity is a marker of arousal and effort and is related to the activity of the norepinephrine in the corpus coeruleus, while N450 indexes inhibitory control and is associated with prefrontal cortex activity. Therefore, we expect either absence of correlation or negative correlation between them.

Methods

Participants

To our knowledge, there are no studies with HSCT in which statistical analyses of EEG/ERP data have been performed that could serve as background information. We estimated the sample size using an a priori method with G-Power software[47,48], which suggested 22 participants for a 0.9 power in a 2-group independent analysis with alpha = 0.05. Thus, to avoid possible loss of participants during preprocessing, we increased the sample size to 50. The participants aged 18–26 years, with a mean age for the depressive group of 23.55 years ($SD = 7.50$), while the control group had a mean age of 20.21 years ($SD = 3.97$). No significant differences were found between the groups ($t\,(41) = 1.854$, $p = 0.071$, $d = 0.567$).

Participants volunteered to participate in the study and were selected by means of the online Spanish version of the Beck II Depression Inventory (BDI-II), which was completed by 370 students from the University of La Laguna (Tenerife, Spain). The BDI-II consists of 21 items with four possible choices that evaluate the severity of each symptom in the past two weeks[39]. A score below 14 indicates no depression states; between 14 and 19 indicates mild symptoms; between 20 and 28 score is considered a moderate state of depression and above 29 is expected to be a severe depression state. The participants also filled out a Spanish version of the Ruminative Response Scale (RRS)[27,28] and a Spanish version of the Snaith-Hamilton of Anhedonia Scale (SHAPS)[49,50]. The RRS is a 22-item scale comprising three factors: reflection, brooding and depression. Items are rated on a four-point Likert-like scale ranging from 1 (never) to 4 (always). The total score ranges from 22 to 88, with higher scores indicating higher degrees of ruminative symptoms. Finally, the SHAPS consists of 14 items with four Likert-scale choices, covering four domains: interests and pastimes, social interaction, sensory experience, and food/drink. In the SHAPS, the values of the items are reversed, that is the higher the score is the less anhedonia symptoms are present.

Twenty-four participants (14 women) with scores below 13 in the BDI-II ($M = 3.87$, $SD = 2.32$) were selected for the control group, (CTL) and twenty-six participants (23 women) with scores above 26 ($M = 32.92$, $SD = 5.96$) were selected for the depressive group (DEP). Finding participants with a BDI score above 29 and without any other clinical disorder or comorbidity was challenging; therefore, we decided to include two more participants with a BDI score of 26, which is considered moderate depression, but it is close to the cut-off of 29 where major depression begins. As expected, the two groups differed in BDI's scores ($t\,(48) = 22.32$, $p < 0.0001$, $d = 6.319$), rumination ($t\,(48) = 13.49$, $p < 0.0001$, $d = 3.736$), and anhedonia: ($t\,(48) = 7.15$, $p < 0.001$, $d = 2.026$), as shown in Table 1.

All participants were right-handed, had normal hearing and normal or corrected-to-normal vision. They filled out a questionnaire about whether they were receiving medication and/or had been diagnosed with clinical disorders. Only those who had no history of substance abuse or other clinical disorders were considered eligible. Of note, none of the participants in the DEP group reported having received a psychiatric diagnosis or were on medication. Once in the laboratory, they signed an informed consent form before starting the experiment. The study was accepted by the IUNE-NEUROCOG board and approved by the ethics committee of the University of La Laguna (code CEIBA 2021–3100), ensuring the protection of participants' rights in accordance with the Helsinki Declaration.

	BDI	Rumination	Anhedonia
CTL	3.87 (2.32)	29.33 (6.25)	51.70 (5.40)
DEP	32.92 (5.96)	64.38 (11.53)	40.50 (5.65)

Table 1. Mean scores and standard deviations (in parenthesis) in the scales for CTL and DEP groups.

Materials, design and procedure

To create the HSCT, 142 sentences were chosen from a larger set obtained from the Spanish standardization of the Hayling test[51], as well as translations of the same test in French and English, and others specifically created for our study, following the same structure but adapted to small dialectal Spanish variants of the Canary Islands (see Supplementary Materials). The selected sentences were validated through a normative study conducted with university students from the community of La Laguna, none of whom participated in the main experiment. We selected sentences in which at least 90% of the participants generated the same word to complete the sentence.

The experiment followed a 2 Group (DEP vs. CTL) x 2 Condition (INIT vs. INHIB) factorial design, with Condition as a within-participant manipulation. During the HSCT, participants' behavioral data (response time and accuracy), EEG, and pupillometric data were recorded for subsequent analysis in both INIT and INHIB conditions.

The HSCT session started with the task instructions and 8 practice trials, followed by the 142 experimental trials presented in a random sequence, which included 98 INIT trials (69%) and 44 INHIB trials (31%). This unbalanced distribution was intended to increase the difficulty of semantic inhibition. Each trial was structured as shown in Fig. 1. The trial began with a gray cross in the center of the computer screen (refresh rate 60 Hz, 1280 × 1024 pixels, 18"), which remained visible for 1 s. The participant then listened to an incomplete sentence through headphones (up to 4s) and was instructed to verbally complete it in two modes, either with a word that obviously fits the context (INIT), or with a word that agrees in gender and number but does not relate to the sentence context (INHIB). Then, 1 s after the end of the incomplete sentence, a green or red circle randomly appeared for 2 s, prompting INIT or INHIB response, respectively.

The experiment was programmed and executed using the Psychopy 3 package[52]. The Google Speech-to-Text and Text-to-Speech[53] application programming interfaces were used for voice-to-text and text-to-voice conversions. In the INIT condition, correct answers (canonical sentence completion word) were assigned a value of 0, and errors were assigned a value of 1 (a word different from the canonical completion). In the INHIB condition, correct answers were computed as 0 (response totally unrelated to the sentence context), 1 was assigned to partially correct responses (different from canonical completion but with some semantic relation to the sentence context), and 3 (canonical word or synonymous). That is, perfect performance in both INIT and INHIB conditions would yield an average score of 0.

EEG recording and preprocessing

For the recording of EEG signals, a Neuroscan amplifier with a sampling rate of 512 Hz and a 62-electrode cap with a standard 10–20 distribution[54] was used. Conductive gel was applied to reduce impedance that was kept below 10 Kohms. Two electrodes were placed above and below the left eye to subsequently identify blinking. Triggers associated with the INIT and INHIB conditions were time-locked to the cue onset, through the parallel port between the stimulus computer and the Neuroscan amplifier. The M1 and M2 electrodes located on the mastoids were used as references. A bandpass filter of 0.1 Hz to 200 Hz was applied online to limit the frequencies. A narrow 50 Hz notch filter was applied to eliminate noise caused by the power grid. Finally, a low-pass filter of 90 Hz was applied to attenuate distortions from higher frequencies. Trials associated with errors detected during task performance were removed as a first step in EEG preprocessing. In addition, four participants were discarded from the analysis, because of technical failures in EEG or voice data collection, being the final sample formed with 21 participants in the CTL group and 25 in the DEP group. The data were re-referenced to the average of all electrodes, followed by automatic preprocessing using MNE-Python[55]. Noisy segments (with amplitudes greater than 190 microvolts or less than 1 microvolt) were discarded; ocular artifacts were removed using VEO electrodes through independent component analysis (ICA), and noise subspace reconstruction (Artifact Subspace Reconstruction–ASR) was applied with a cutoff parameter of 15[56]. The data

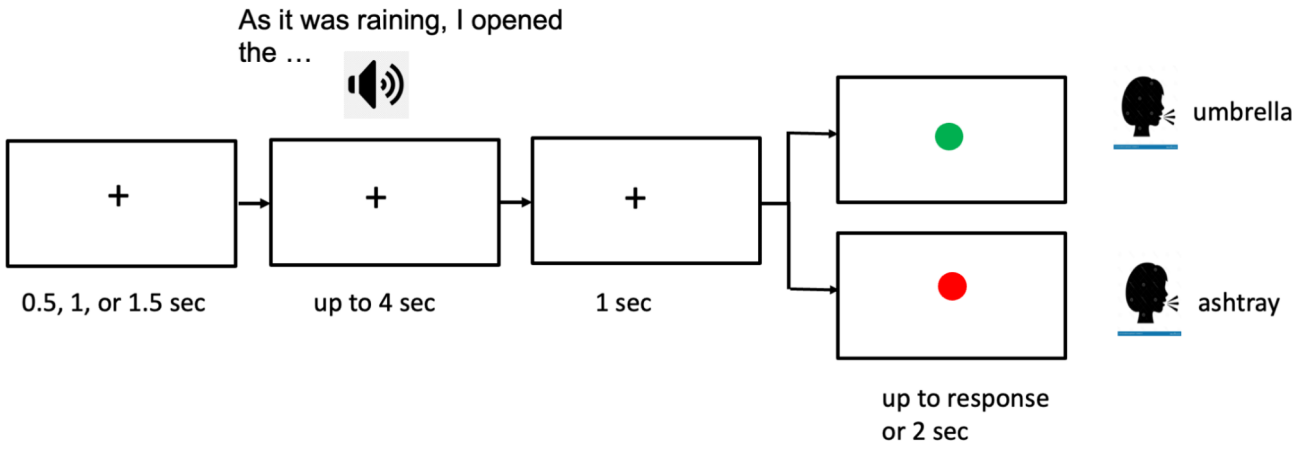

Fig. 1. Outline of INIT (green cue) and INHIB (red cue) trials in the HSCT. The EEG trigger was time-locked to the onset of the color cue.

was then segmented ranging from −200 ms to 800 ms. A baseline of -200 ms before each trigger was used as a reference measure and subtracted from the entire interval.

Pupil dilation (PD)

A pc-mounted Tobii 4 C eye-tracking device based on pupil reflection using infrared light was used to capture variations in pupil dilation (PD) in the left eye, with a tracking frequency of 90 Hz. The synchronization of this device with the onset of the INIT or INHIB cues was achieved using the Lab Streaming Layer (LSL) library[57], through an internet-based local network. Data from 6 participants (2 CTL and 4 DEP) were discarded from the analyses because of failures in the device so a total of 22 CTL and 22 DEP participants were analyzed.

Plan of analyses

Our statistical analysis plan aimed to evaluate the effects of two within-participant conditions of the HSCT (INIT and INHIB) on two groups (CTL and DEP), for the behavioral, ERP and PD measures ensuring robustness and reliability of the results. Normality and homogeneity of variances for the dependent variables were assessed using the Shapiro-Wilk and Levene's tests, respectively. For data meeting these assumptions, a Condition x Group mixed ANOVA was performed, followed by Tukey post-hoc tests when necessary. For the pupillometry and the hemisphere effects, the differential value (INHIB - INIT) was calculated to be used as the dependent measure, and subsequent normality and homogeneity checks were performed, using simple ANOVA. If the normality assumption was met but homogeneity of variances was not, we applied Welch's ANOVA. If neither assumption was fulfilled, we employed the non-parametric Mann-Whitney U test. This structured approach was complemented by multiple comparison corrections when needed.

Results

Behavioral results

Table 2 shows the mean percentage of errors and response time (RT) in the HSCT for both CTL and DEP groups.

The ANOVA on the percentage of errors showed significant main effects of Group (F (1, 47) = 6.72, $p < 0.01$; $\eta^2 = 0.125$), with the DEP group making more errors than CTL group, and a main effect of Condition (F (1, 47) = 11.53, $p < 0.001$; $\eta^2 = 0.197$), with more errors for INHIB condition than INIT, but no significant interaction was found (F (1, 47) = 2.83, $p > 0.05$). The ANOVA for RT did not show any significant difference between conditions (F (1, 47) < 1), groups (F (1, 47) = 1.273, $p = 0.26$), nor the interaction (F (1, 47) = 3.34, $p = 0.07$).

ERP results

In the preliminary temporo-spatial cluster analyses[58] over the Grand Average of condition (INHIB vs. INIT) a fronto-central cluster of electrodes emerged as significant in the CTL group, and a parieto-occipital cluster was significant for both CTL and DEP groups (see Fig. 2).

Fronto-central N450. The large fronto-central cluster of 13 electrodes [Fp1, Fp2, F3, F4, F7, Fz, F2, AF3, AF4, F5, AF7, AF8, Fpz] was averaged, showing a negative-going waveform in the 444–524 ms time window larger for INHIB than INIT condition, especially for the CTL group, as shown in Fig. 2(A). This waveform, according to its timing and distribution, can be identified as the N450 component[7–10], and was followed by a late slow positive-going waveform between 600 and 800 ms, probably associated with response selection processes. The mixed ANOVA conducted on the N450 time window, revealed a highly significant main effect of Condition (F(1, 45) = 39.71, $p < 0.001$) with a large effect size ($\eta^2 = 0.468$), indicating larger amplitude for INHIB than INIT trials, and a significant main effect of Group (F(1, 45) = 4.87, $p < 0.05$), with smaller effect size ($\eta^2 = 0.097$), consisting of larger N450 amplitude for CTL than DEP participants. However, the interaction Group by Condition did not reach significance (F (1, 45) = 1.62, $p = 0.208$; $\eta^2 = 0.034$). Concerning the 600–800 ms time window, only a main effect of condition was observed (F (1, 45) = 32.58, $p < 0.0001$; $\eta^2 = 0.291$).

Post hoc t-tests performed separately for the two groups, confirmed a larger N450 amplitude for INHIB than INIT trials, for both CTL (t (24) = -5.309, $p < 0.0001$; $\eta^2 = 0.232$) and DEP (t (21) = -3.68; $p < 0.01$, $\eta^2 = 0.092$) participants. However, between-group comparisons revealed that the enhanced INHIB-related N450 was significantly larger for the CTL group than for the DEP group (t (44) = -2.479, $p < 0.05$; $\eta^2 = 0.116$), whereas the two groups did not differ in the INIT-related N450 (t(43.5) = -1.452, $p = 0.153$). In other words, the DEP group showed a more reduced N450 modulation by inhibitory demands in comparison with the CTL group.

To further investigate the differences between the CTL and DEP groups, we performed additional analyses of the N450 component, using the INHIB - INIT differential values as the dependent variable, and including brain hemisphere as a new factor. Initially, we explored hemispheric differences using the electrodes

		Errors (%)		RT (ms)	
GROUP	CONDITIONS	Mean	SD	Mean	SD
CTL	INIT	9.20	3.90	977	334
	INHIB	13.40	15.80	1046	367
DEP	INIT	11.80	4.80	938	265
	INHIB	24.30	18.20	887	343

Table 2. Means and standard deviations in errors (%) and response time (RT) in milliseconds for groups (CTL and DEP) in the INIT and INHIB conditions of the HSCT.

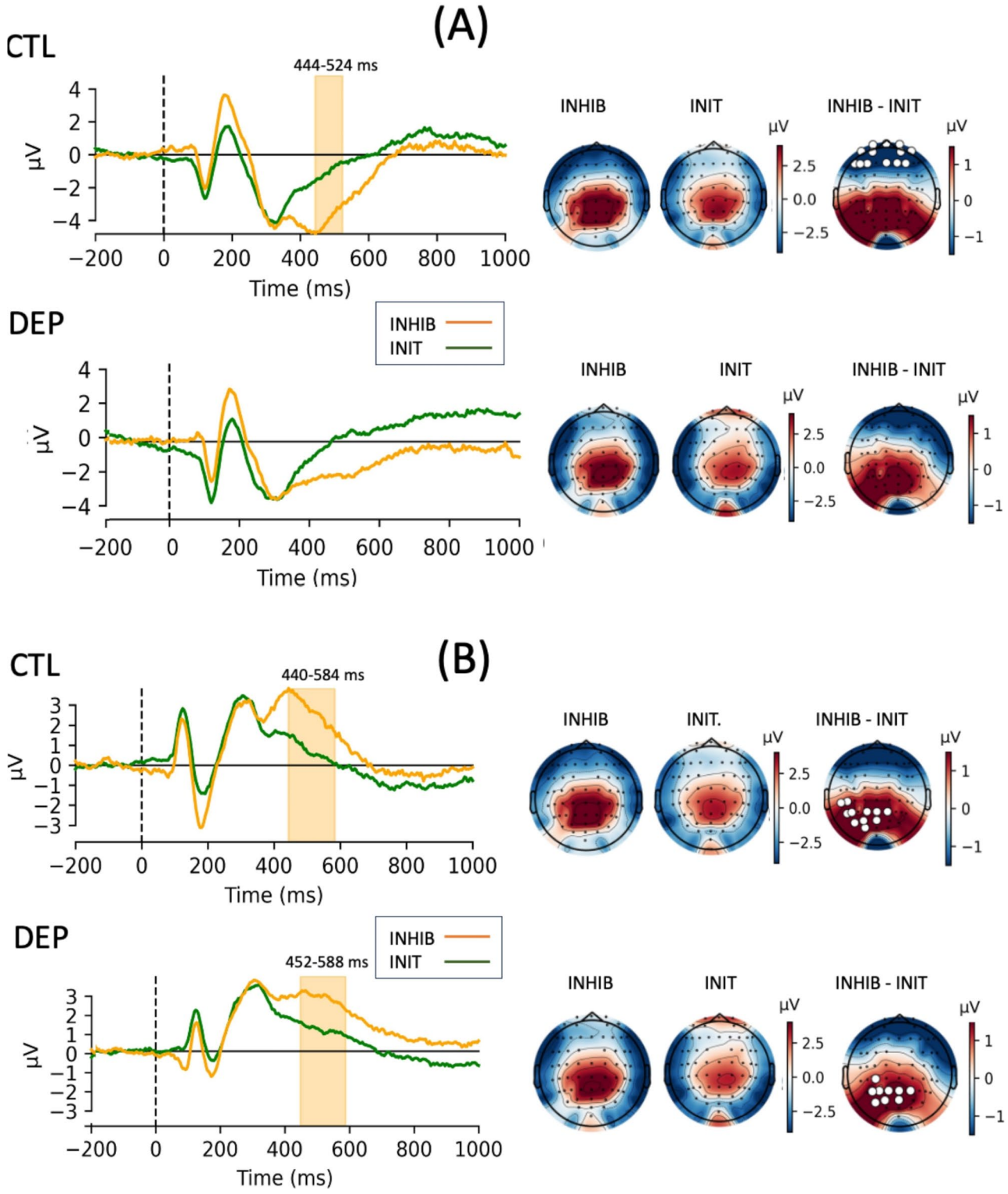

Fig. 2. ERPs of INIT and INHIB conditions, depicted for the CTL and DEP groups separately. (**A**) Averaged of 13 fronto-central electrodes in which the effect of condition was only significant in the CTL group. (**B**) Averaged of parieto-occipital electrodes in which the effect of condition was significant in both the CTL (18 electrodes) and the DEP group (9 electrodes).

corresponding to the previously mentioned N450 cluster, except the central electrodes Fz and Fpz. Specifically, the left hemisphere (LH) included the electrodes: Fp1, F3, F7, F1, AF3, F5, AF7, and the right hemisphere (RH) included the electrodes: Fp2, F4, F2, F8, AF4, F6, AF8. Since this analysis did not yield significant hemisphere effects, we performed additional exploratory analyses, based on previous research[59], which showed that a few

fronto-central electrodes (F2, Fz FC2) were sufficient to differentiate CTL and DEP participants in resting state. Thus, we tested a few combinations of homologous right and left frontal electrodes and obtained significant effects by contrasting F3 and FC3 for the left hemisphere, and F4 and FC4 for the right hemisphere. Specifically, the ANOVA conducted in the highlighted time window from 390 to 480 ms revealed a significant Group x Hemisphere interaction (F (1, 45) = 4.079, $p < 0.05$; $\eta^2 = 0.08$), depicted in Fig. 3. Pairwise comparisons obtained a more reduced activity in the left hemisphere of the DEP compared to the CTL group (t (44.9) = 2.38, $p < 0.05$, $\eta^2 = 0.106$), while the groups did not differ in the right hemisphere (t(44.8) = 0.344, $p = 0.732$).

Parieto-occipital positivity. A cluster of widespread late positivity was obtained at parieto-occipital sites between 400–600 ms, partially overlapping the N450 temporal window. The cluster comprised 11 electrodes in the CTL group [O1, P7, Pz, CP5, P1, P2, PO3, P5, TP7, PO7, POz], and 9 electrodes in the DEP group ['P3', 'Pz', 'P1', 'P2', 'CP3', 'PO3', 'P5', 'PO7', 'POz']. A Group x Condition ANOVA was conducted for the cluster of 9 electrodes shared by the two groups There was a robust main effect of Condition (F (1, 45) = 73.56, $p < 0.001$; $\eta^2 = 0.625$), corresponding to the larger positive waveform for INHIB than INIT trials. However, neither the main effect of Group (F (1, 45) = 1,21, $p = 0.27$) nor the Group x Condition interaction (F(1,45) = 0.25, $p = 0.61$) produced any significant effect. That is, the strong modulatory effect of INHIB compared to INIT at parietal sites, was similar in the DEP and CTL groups, as Fig. 1(B) illustrates.

Source analysis

Source analysis of the INHIB minus INIT trials differences was performed with MNE Python 1.4.2 using eLORETA for CTL and DEP groups, revealing a main source of activation in the orbitofrontal cortex (BA 10, 11). Figure 4(A) shows the time course of source activation for both groups separately. A detailed analysis of the temporal course of activation for the sources confirmed the significant difference between groups, reported in the N450, at the left frontal pole, in a time window between 300 and 500 ms ($p < 0.0001$). Specifically, the DEP group showed a reduced activity in comparison to the CTL group in this region, as shown in Fig. 4(B).

Pupil dilation analysis

Individual pupillary dilation (PD) measurements were recorded in arbitrary units (AU), which were obtained as relative values calibrated individually for each participant. To ensure a standardized reference frame across subjects before averaging, these measurements were normalized to a 0–1 range using the MinMaxScaler function from the scikit-learn Python library (version 1.3.0)[60]. Following normalization, the data were segmented into epochs spanning from 200 milliseconds before stimulus onset to 800 milliseconds post-stimulus. The interval from − 200 milliseconds to stimulus onset (0 milliseconds) was used for baseline correction. Figure 5 illustrates the evolution of pupil dilation in the conditions and groups over time. Panel A shows the PD of the CTL group, which suggests stability over time and no appreciable differences between the INHIB and INIT conditions. In contrast, panel B clearly shows in the DEP group that the INHIB condition induces a consistently higher pupil dilation compared to the INIT condition over the same time period. Panel C includes the INHIB - INIT differential PD for both groups over time, and Panel D further qualifies these differences showing their distribution for CTL and DEP in the 320–450 ms time window. These effects were corroborated by the ANOVA on the INHIB - INIT differences in PD which yielded a significant effect of Group (F (1, 42) = 4.118 $p < 0.05$, $\eta 2 = 0.089$). That is, individuals in the DEP group showed markedly greater PD reactivity to semantic inhibition demands than the CTL group.

Correlations

We calculated correlations between self-report scales and the ERP and pupillometric measures for the whole sample of participants. The most relevant Pearson correlations were between the N450 measure for INHIB at

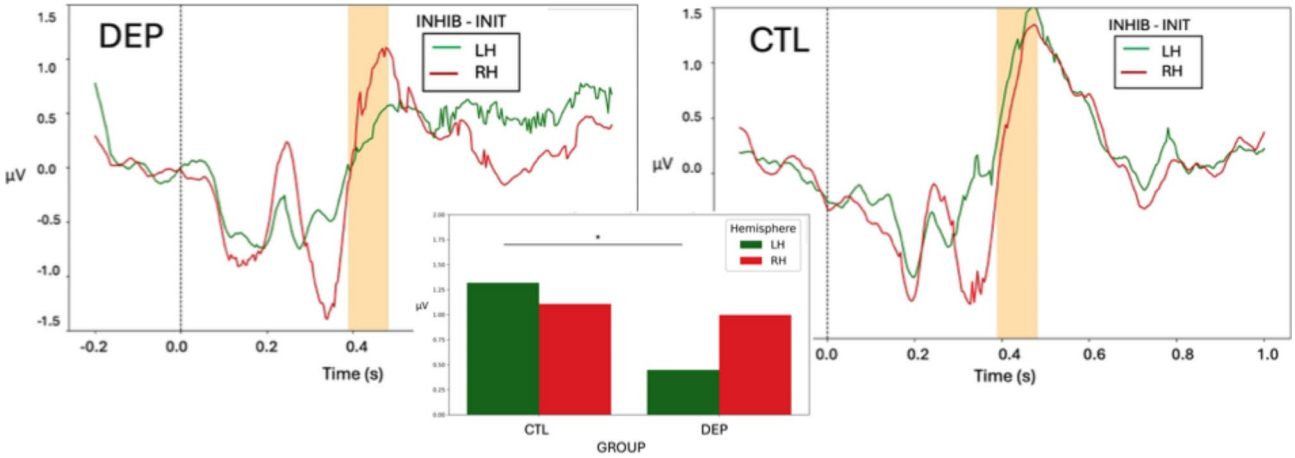

Fig. 3. Hemisphere activity (INHIB minus INIT) for the DEP (left) and the CTL group (right). The DEP group showed significantly less activity in the left hemisphere (electrodes F3, FC3) than the CTL (central panel), while the groups did not differ in the right hemisphere (electrodes F4, FC4).

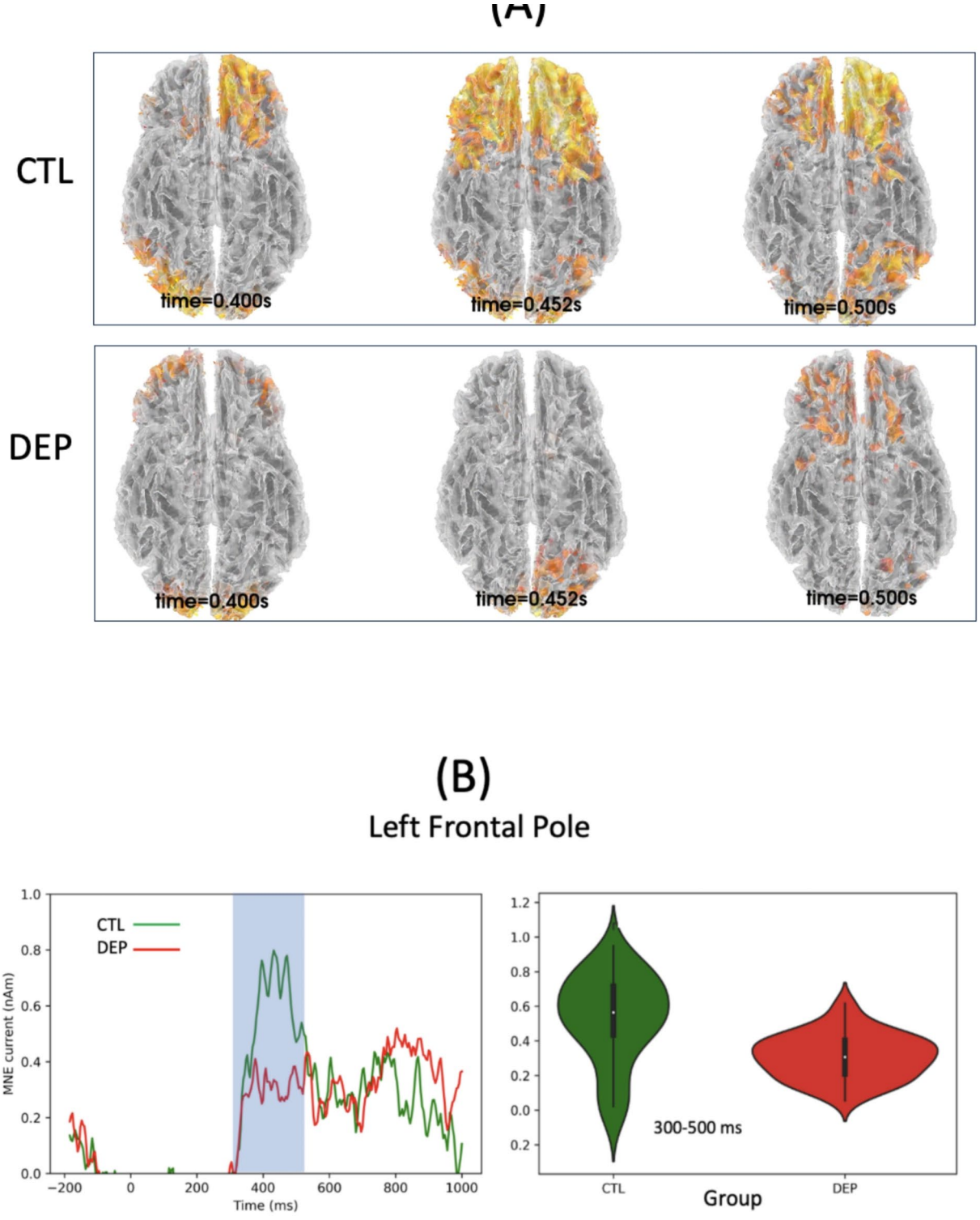

Fig. 4. (**A**) Time course of INHIB – INIT difference in source activations for the CTL and the DEP groups in the time window 400–500 ms. (**B**) Time course of activation at the left frontal pole for CTL and DEP groups, and distribution of their average values at the time window 300–500 ms ($p < 0.001$).

fronto-central sites and rumination ($r = 0.402$ $p < 0.005$), and anhedonia scores ($r = -0.588$, $p < 0.0001$). That is, higher rumination and anhedonia are associated with a reduction of fronto-central activity for inhibition trials. Notably, the N450 for INIT trials also positively correlated with rumination ($r = 0.302$, $p < 0.04$) and negatively with anhedonia ($r = -0.373$, $p < 0.01$; note that for the SHAPS, higher scores correspond to less anhedonia). However, in Fig. 6 it can be seen that the majority of participants who showed high levels of anhedonia and,

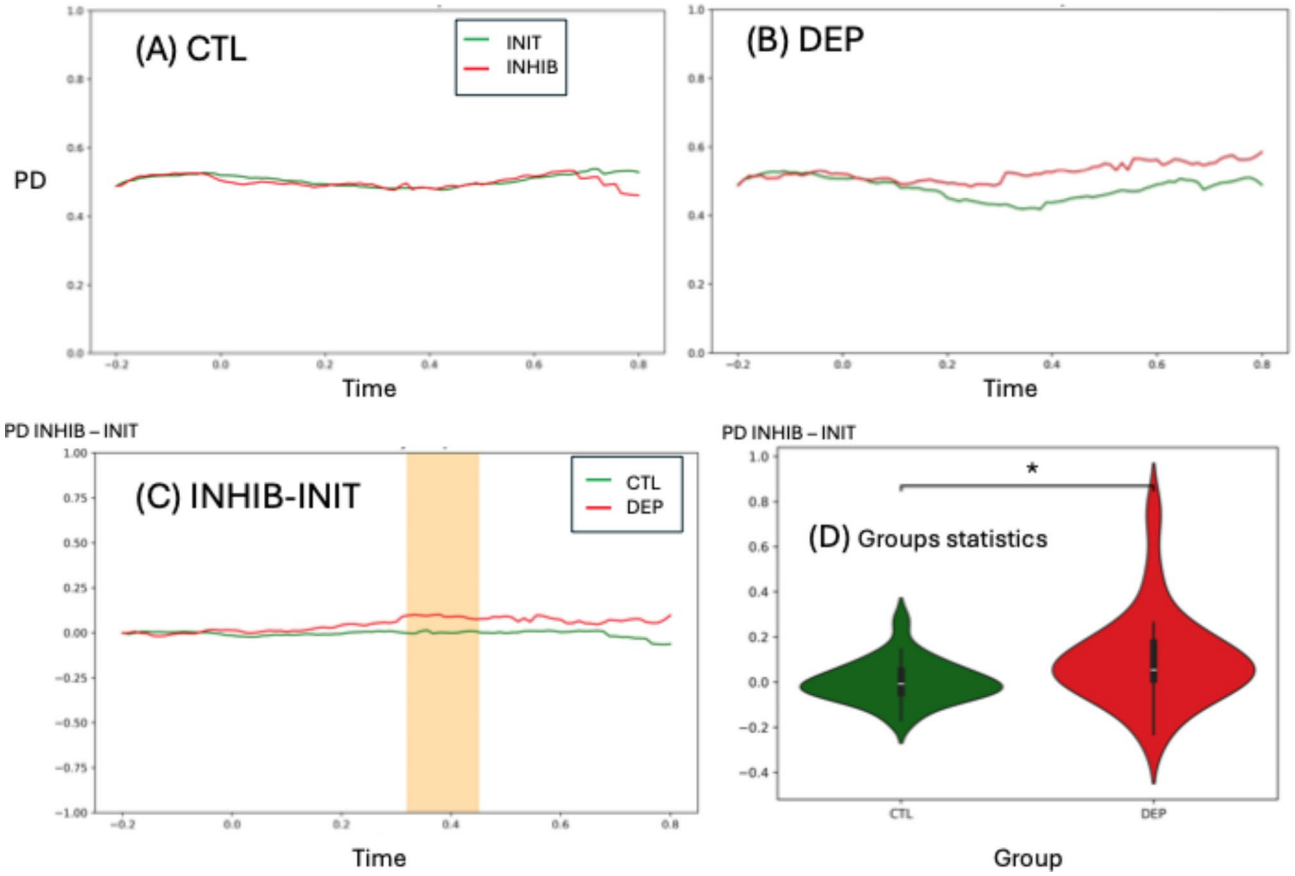

Fig. 5. (**A**) Pupil dilation for INIT and INHIB trials for CTL group (**B**) Pupil dilation evolution for INIT and INHIB trials for the DEP group. (**C**) Pupil dilation evolution for the differences between INHIB minus INIT trials for CTL and DEP, between 320 and 450 ms. Both groups differed significantly ($p < 0.05$) on this window.

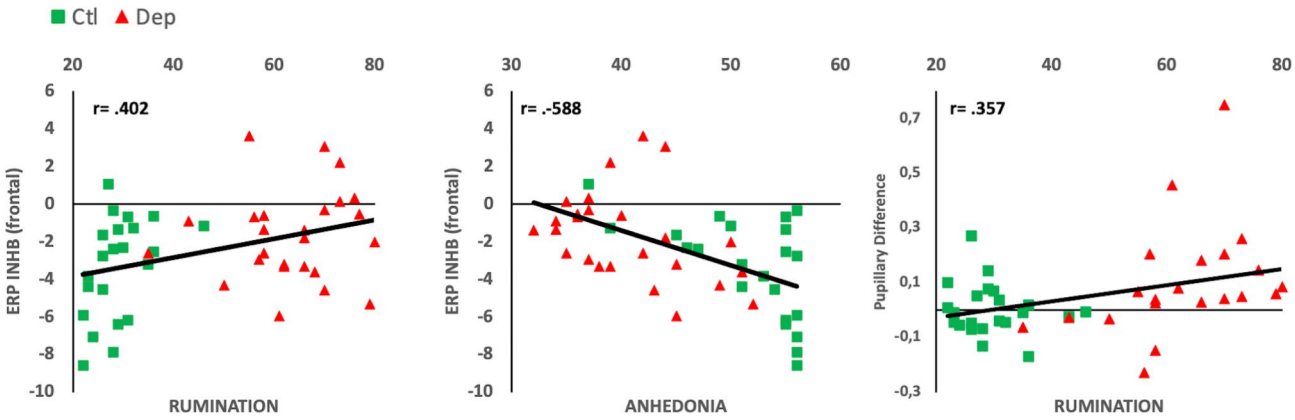

Fig. 6. Scatterplots for the correlations between fronto-central N450 inhibition trials and self-report rumination and anhedonia (left and center, respectively), and between pupil dilation (INHIB - INIT) and rumination (right). Note that DEP and CTL participants tend to cluster in opposite ranges of rumination and anhedonia scores, especially on rumination.

especially, high levels of rumination, were individuals in the DEP group, whose scores are clustered in the extreme range of both scales, whereas the scores of participants in the CTL group are more widely distributed in the scales. To test this idea, correlations between self-report scales and fronto-central N450 measures were calculated separately for the groups. As expected, rumination and anhedonia remained highly correlated for the INHIB trials in the CTL group, whereas correlations were small and non-significant in the DEP group due to their clustering (see Supplementary Materials, Table S2). This is not surprising, since we selected the DEP group

for its high scores on depression, which in turn correlates strongly with rumination ($r=0.91$, $p<0.0001$), and to a lesser extent with anhedonia ($r=0.71$, $p<0.0001$). As for the pupillometric measures, we first calculated the difference INHIB – INIT in pupil dilation in the 320–450 ms time window, and we obtained significant correlations with rumination ($r=0.357$, $p<0.05$) and with the INHIB fronto-central component ($r=0.314$, $p<0.05$), indicating small but significant relationship between physiological arousal and both participants' rumination and inhibition-related neural dynamics. Correlations between self-report scales and accuracy (% errors) in Inhibition and initiation trials are shown in Supplementary Materials (S3).

Discussion

This study investigated the cognitive and neurophysiological differences between college students with depressive states and non-depressive controls while they performed a modified HSCT, in which the demand to complete a sentence with a related word (INIT) or non-related word (INHIB), was randomized on a trial-by-trial basis. The co-register of EEG and pupillometry measures, offered an opportunity to simultaneously track the brain dynamics and the physiological arousal of participants in a task with high semantic inhibition demands.

Inhibition and initiation trials differed in most measures in the experiment. That is, lower response accuracy, and greater waveform of late frontal negativity associated with prefrontal sources were observed in the INHIB than in the INIT trials. Furthermore, the main goal of contrasting depressive and control participants, yielded several relevant results. First, the DEP group performance on INHIB trials was lower, as they made more errors than the CTL group. Second, the frontally distributed negativity, identified as N450 was reduced in DEP compared with CTL on both INHIB and INIT trials, suggesting that individuals with depression have impaired associative and inhibitory semantic memory processes. Furthermore, the most conspicuous difference between DEP and CTL was observed in the INHIB condition, indicating that people with depression have particular difficulty suppressing concepts under the inhibitory demands of the HSCT. Third, the reduction of N450 for inhibition trials in DEP compared to CTL was more pronounced in the left hemisphere than in the right hemisphere. Fourth, source estimation confirmed INHIB-associated frontopolar activity (BA 10, 11) in both CTL and DEP. However, the two groups differed in that the CTL showed bilateral frontopolar activity, whereas the DEP showed reduced left hemisphere frontopolar activity. Fifth, pupillary dilation was task-sensitive only in the DEP group (INHIB > INIT) during a time window between 300 and 450, partially overlapping the cortical reaction (N450). Finally, self-reported rumination and anhedonia correlated with the neural activity at fronto-central electrodes in the INHIB condition and to a lesser extent in the INIT condition. In addition, there was a significant correlation between neural activity and pupil dilation, sensitive to inhibition.

Note that the unbalanced number of INIT and INHIB trials (69% vs. 31%) in our materials could potentially be a confounding variable, as the former are more predictable, and the latter could be associated with surprise. In previous decision-making studies in which the probability of events was manipulated it has been reported that surprise caused by unexpected events modulates differentially the N2 and P3 components of the ERPs[61] and the pupil dilation[62]. However, in the current HSCT no modulation of the N2 and P3 components was observed, suggesting that this factor has a negligible effect on the brain dynamics associated with our task. On the other hand, pupil dilation was not a general index of surprise, as it was not sensitive to INHIB trials in the CTL group, but just a distinctive marker of depression. Therefore, we can assume that the ERP and pupillometry effects obtained in this study refer to our experimental factors of HSCT Condition and Group.

Semantic inhibition and depression

The HSCT employed here focuses on semantic inhibition processes and, therefore, we expected individuals with depressive states to differ in performance and neural dynamics from nondepressed individuals. This was the case, as the CTL and DEP groups showed significant differences in both behavioral and ERP data of the HSCT. As for ERP data, a widespread fronto-central N450 waveform was observed, with a larger amplitude for INHIB trials compared to INIT trials. This suggests that this component was particularly sensitive to semantic inhibition. Notably, this finding aligns with the commonly reported N450 in studies involving the Stroop task, where it demonstrated sensitivity to the color incongruence condition and has been frequently linked to the functioning of the ACC and other prefrontal structures[20–23]. In this study, the enhanced N450 modulation by INHIB trials compared to INIT trials, was observed in both CTL and DEP participants. However, the two groups differed in that CTL showed significantly greater N450 than DEP in the INHIB condition, whereas the group difference was attenuated and non-significant in the INIT condition. In summary, individuals experiencing depression have more reduced neural activity associated with semantic inhibition than the controls. In addition, comparison between selected right- and left-frontal electrodes highlights that the disparity in inhibition-related N450 between the two groups of participants was more pronounced in the left hemisphere, where DEP participants showed less discernible differential effect of conditions. In other words, while frontal activity in CTL participants is bilateral, in DEP participants the activity is right lateralized.

The estimated neural source of the N450 was identified as the prefrontal cortex, particularly the OFC (BA 10, 11), aligning with previous neuroimaging findings in the context of the HSCT[17–19]. Furthermore, the source estimation of our N450 substantiated diminished activity in the left-frontal hemisphere within the DEP group, suggesting a functional imbalance between hemispheres in participants with depression. The left hemisphere, particularly the prefrontal cortex, is involved in cognitive control and regulation of emotions and its hypoactivation may reflect a reduced ability to regulate negative emotions or to initiate adaptive responses to stress[45,46]. This could lead to difficulty in overriding negative thoughts, feelings, or memories, contributing to depressive symptoms like rumination. These outcomes resonate with analogous hemispheric imbalance patterns observed in individuals with major depression, where there is evidence of right-hemisphere hyperactivity and/or left-hemisphere hypoactivity in resting state[40] or during performance of inhibition tasks[41,45,46].

Cognitive effort differences

Pupillometric results also revealed significant differences between groups, although the differential pattern of pupil dilation markedly differed from that obtained in the ERP data. First, in the ERP the neural reactivity to INHIB trials was larger for CTL than DEP, whereas the reverse was true for pupil dilation. That is, in the CTL group the pupillary reactivity was stable over time and similar for INIT and INHIB trials, while in the DEP group pupil dilation was higher for a relatively long period for INHIB trials, indicating persistent cognitive effort or arousal associated with inhibition demands[22–25]. Second, in the DEP group the pupil response slightly preceded (320–450 ms) and partially overlapped the ERP effects (440–524 ms). Third, the pupil dilation has low but significant correlation with the fronto-central activity of the ERP, suggesting that the physiological pupil reaction and the neural activity are moderately associated. In a comparable study with the emotional Stroop task[63], also found correlation between PD and some inhibition-related components of the ERP (P1/N1 and P3). Pupil dilation is considered an index of activity of the brainstem's locus coeruleus and the norepinephrine system, which is functionally related to alert, arousal, attention and mental effort, involving broadly distributed connections with the prefrontal cortex and other brain areas[24]. This suggests that participants with depression have altered the norepinephrine modulation associated with inhibition-demanding trials.

Self-report measures and N450

Self-reported rumination and anhedonia, two hallmark symptoms of depression[35,64,65], correlated with N450 in INHIB trials, suggesting that they are associated with semantic inhibition deficits. First, the difficulty to suppress negative thoughts or ruminate in our participants with depression is associated with alterations in neural processes of semantic inhibition, as the DEP group who obtained the highest scores in rumination also tends to reduce the N450 during inhibition trials, which is consistent with previous evidence that rumination correlates with ERPs inhibition-related signatures[21,31] and with activity of neural networks of inhibition[32]. Second, although anhedonia is generally attributed to dysfunction in the reward system of the brain, it has also been linked to altered executive functions in the prefrontal cortex[35], including an altered GABAergic system, responsible for inhibition[64]. This would explain that, in our study, self-reported anhedonia also was associated with semantic inhibition, indexed by the N450 in INHIB trials. Notably, rumination and anhedonia also correlated with N450 in INIT trials, suggesting that these depression-related traits are associated not only with inhibition but also with associative processes in semantic memory[17].

This study has some limitations. First, the selection of DEP and CTL participants was based on an online self-report scale, rather than on face-to-face interviews (e.g., the MINI International Neuropsychiatric Interview), which allow for more accurate assessment of mental health problems. Second, data collection for this study was conducted during the COVID pandemic, including periods of lockdown, which likely increased the number of individuals with depressive symptoms[66,67]. Third, as a consequence of the above statements, the results obtained in this study with college students suffering from depressive states cannot be generalized to other populations, nor to psychiatric patients with diagnosed major depression. However, the results seem valuable, as the DEP group differed from the CTL group in all kinds of semantic inhibition indices, including lower performance, and altered brain dynamics, which in turn correlated with anhedonia and rumination. Fourth, the gender distribution was unbalanced between the groups. The DEP group was predominantly composed of women, whereas the CTL group had a more balanced gender composition. This discrepancy may introduce confounding variables that could influence the results and the generalizability of the conclusions. It should be noted that most of our participants were from psychology faculty, which may have contributed to this gender imbalance. In addition, the higher prevalence of depression among women compared to men could also be reflected in the composition of our depressive group. Future research should consider a more balanced gender distribution to improve group comparability and external validity.

Conclusions

EEG-pupillometric co-registration during HSCT demonstrates how college students with depressive states differ from a control group of the same population in the management of semantic processes (both activation and inhibition) in sentence completion contexts. Specifically, modulation of the frontal N450 component of ERP, which indexes semantic conflict and inhibition, was reduced in individuals with depression, indicating less efficient semantic inhibition. In addition, the participants with depression showed a functional imbalance of the prefrontal cortex, consisting of left hemisphere hypoactivity, as indicated by ERP and the estimated source in the orbitofrontal cortex. The fact that the N450 component in inhibition trials correlates with self-reported measures suggests that semantic inhibition deficits may be associated with some of the more distinctive symptoms of depression, that is rumination and anhedonia. The peripheral measure of pupil dilation indicates that individuals with depression expend more effort or increase arousal level on semantic inhibition demands, and this effect is associated with parieto-occipital activity in the EEG.

Data availability

All stimuli, the experimental data and the scripts used for their collection and analysiscan be viewed and downloaded from the Open Science Framework (OSF).Psychopy Hayling task:https://drive.google.com/file/d/1gu-0J2pu_f1-zRHTtU420wkhUY-rxD0p5/view, MNE-Python scripts for preprocessing data: https://drive.google.com/drive/folders/1S2tUSGVAKQtD9cb_RYIA-PuHeNeANMbX?usp=sharing.

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D.J.: conceptualization, validation, methodology, formal analysis, funding acquisition, resources, investigation, writing—review and editing. J.L.P.: resources, data curation, methodology, writing—review and editing. I.P.: conceptualization, validation, methodology, resources, funding acquisition, project administration, supervision, review and editing. MDV.: conceptualization, validation, methodology, resources, funding acquisition, project administration, writing—original draft, writing—review and editing, supervision.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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