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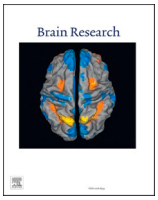

Neural oscillations modulation during working memory in pre-manifest and early Huntington's disease

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ABSTRACT

Introduction: We recently demonstrated specific spectral signatures associated with updating of memory information, working memory (WM) maintenance and readout, with relatively high spatial resolution by means of high-density electroencephalography (hdEEG). WM is impaired already in early symptomatic HD (early-HD) and in pre-manifest HD (pre-HD). The aim of this study was to test whether hdEEG coupled to source localization allows for the identification of neuronal oscillations in specific frequency bands in 16 pre-HD and early-HD during different phases of a WM task.

Methods: We examined modulation of neural oscillations by event-related synchronization and desynchronization (ERS/ERD) of θ, β, gamma low, γ_{LOW} and γ_{HIGH} EEG bands in a-priori selected large fronto-parietal network, including the insula and the cerebellum.

Results: We found: (i) Reduced θ oscillations in HD with respect to controls in almost all the areas of the WM network during the update and readout phases; (ii) Modulation of β oscillations, which increased during the maintenance phase of the WM task in both groups; (iii) correlation of γ_{HIGH} oscillations during WM task with disease burden score in HD patients.

Conclusions: Our data show reduced phase-specific modulation of oscillations in pre-HD and early-HD, even in the presence of preserved dynamic of modulation. Particularly, reduced synchronization in the θ band in the areas of the WM network, consistent with abnormal long-range coordination of neuronal activity within this network, was found in update and readout phases in HD groups.

1. Introduction

Huntington disease (HD) is a progressive, genetically determined, neurodegenerative disease associated with a combination of cognitive, motor, and psychiatric symptoms. A cytosine–adenine–guanine (CAG) repeats expansion (≥36) within the huntingtin gene is the molecular cause of the disease and it can be identified years before the onset of first symptoms of HD (Roos, 2010; Rosas et al., 2008).

Cognitive functions can be impaired years before motor symptoms, playing a crucial role for patients' autonomy and quality of life (Roos, 2010). One of the earliest and most affecting symptom in the cognitive domain is the reduction of processing speed and efficacy of executive functions (Lemiere et al., 2004).

Working memory (WM) is the ability to keep in mind information and retrieve them after a short period of time, and is one of the first cognitive functions to decline in HD (Lemiere et al., 2004). Imaging

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studies associated HD with a decreased coupling in (the) fronto-parietal network(s), which is consistently activated during WM tasks. This effect is relevant even in pre-manifest or early stages HD (Lahr et al., 2018). A cortical gray matter morphometry study, performed in a large sample of pre-HD individuals showed that executive components of WM (i.e., manipulation of information) was associated with thinning in elements of an executive WM network, including the inferior parietal cortex and bilateral rostral prefrontal cortex (Harrington et al., 2014). A recent resting state fMRI study, adopting dynamic functional network connectivity, showed decreased connectivity between the putamen and medial prefrontal cortex in pre-manifest HD that was significantly associated with cognitive performance (Espinoza et al., 2018). Furthermore, specifically in a WM task, resting state fMRI showed in HD mutation carriers differential connectivity compared with controls across almost the entire WM network (Lahr et al., 2018).

One of the most popular task to evaluate WM, is the n-back task (Kirchner, 1958), consisting in the presentation of a series of stimuli to the participants, that have to indicate whether the current stimulus (probe) matches the stimulus presented n-stimuli back in the series. Several studies have reported impairment in WM tasks in early symptomatic HD (early-HD) participants (Lawrence et al., 1996), but also in pre-manifest HD, carrying the mutant huntingtin gene, (pre-HD) compared with controls (Lemiere et al., 2002).

In a recent study (Semprini et al., 2020), our group evaluated spatial location and temporal dynamics of neural oscillations of young healthy subjects associated with the different phases of WM (update, maintenance, readout) in the n-back task, by means of an accurate reconstruction of neural activity in the brain through high-density electroencephalography (hdEEG). We demonstrated specific spectral signatures associated with updating of memory information, WM maintenance, and readout, with relatively high spatial resolution. Particularly, we found, widely distributed increased theta event-related synchronization (ERS) and smaller beta ERS during the update and readout and decreased theta ERS and increased beta ERS and focally increased oscillations in gamma low and gamma high bands in the maintenance phase (Semprini et al., 2020).

To our knowledge, even if functional and effective connectivity changes have been highlighted in pre-manifest and manifest HD using blood oxygen level–dependent, task-based, or resting- state functional magnetic resonance imaging (Espinoza et al., 2018; Wolf et al., 2012), no study employed high-density electroencephalography (hdEEG) coupled to source localization to obtain information on spatial distribution and temporal dynamics of neural oscillations associated with different phases of the WM in HD patients. Altered oscillatory activity has been described in resting EEG in HD since early stages (Painold et al., 2011). Particularly, relative to the band of interest whose modulation was associated with specific phases of the WM task in our previous study (Semprini et al., 2020), reduced relative power of the theta band was observed in pre-manifest HD in resting state EEG as compared to controls (Ponomareva et al., 2014). Decreased theta power was also observed from early to late stages of the disease with a correlation between decrease of theta power and increasing cognitive and motor decline (Painold et al., n.d.). However, to the best of our knowledge, the impact of HD on EEG oscillations in the different phases of the WM task (updating of memory information, WM maintenance, and readout) has not been explored so far.

The aim of the present study was to test whether high-density electroencephalography (hdEEG) coupled to source localization allows for the identification of neuronal oscillations in specific frequency bands in pre-manifest and very early manifest HD during determined phases of a WM task. We expect that pre-manifest and early Huntington's disease already show decreased theta oscillation during the update and readout phases of WM task, mainly in the fronto-parietal areas. Identifying focally specific band oscillations in the phases of the WM task in patients with HD will be instrumental for developing personalized neuromodulation treatment of cognitive dysfunction, since the pre-symptomatic or early stage.

2. Materials and methods

2.1. Subjects

Sixteen patients with genetically confirmed HD participated in this study. The mean ± SD age of the patients was 44 ± 12.26 years. Our group included 7 pre-HD patients, and 9 early-HD patients. The mean disease duration for early-HD subgroup ranged between 12 months and 8 years (mean ± SD, 3.2 ± 2.6 years). Demographic and clinical details are summarized in Table 1. Motor, psychiatric and cognitive clinical evaluation was performed using the Unified Huntington's Disease Rating Scale (UHDRS). The disease burden score (CAP score) was computed by multiplying age at study entry (Age0) by a scaling of the CAG repeat length ($CAP = Age0 \times (CAG - 33.66)/432.3326$)(Zhang et al., 2011).

The following inclusion criteria were applied: (i) Positive genetic testing for all participants in the HD group. For early-HD only, the following inclusion criteria were applied: (i) UHDRS Total Motor Score $\geq$ 5; (ii) UHDRS Total functional capacity (TFC): 7–13. For all participants in the HD group, the following exclusion criteria were applied: (1) history of neurological conditions other than HD or previous neurosurgery to the brain (2) Mini-Mental State Examination score $<$ 24, (3) no interest in the study and (4) retinal damage, or other eye problems, which could prevent subjects from seeing the pc screen.

For the control group (CTRL), we recruited 16 neurologically intact, right-handed subjects, matched for gender and age (mean (SD) age 39.13 (±12.07) years).

All subjects provided written informed consent. The study conforms to the standard of the Declaration of Helsinki and was approved by the institutional ethical committee (CER Liguria Ref.1293 of September 12th, 2018).

2.2. Cognitive task and experimental setup

We used an n-back working memory (WM) task (with n = 2, 3) as in (Hoy et al., 2015) and (Semprini et al., 2020). Each subject was instructed to check random letters (A, B, C, D, E, F, G, H, I, O) that appeared on a screen in front of her/him, and to respond with a button press when the currently presented letter (stimulus) corresponded to the letter presented n trials earlier (probe). Each letter appeared on a screen for 500 ms with a 2000 ms delay between stimuli presentations. For more detailed information, refer to (Semprini et al., 2020).

For hdEEG recording we used a 128-channel EEG recording system (actiCHamp, Brain Products), equipped with a trigger box for handling external events. We collected hdEEG data at 1000 Hz sampling frequency, using the electrode FCz as physical reference. We also collected horizontal and vertical electrooculograms (EOG) from the right eye for

Table 1
Demographic, genetic and clinical data from HD patients.

Patient	Age	Gender	CAG	UHDRS I
Premanifest 1	30	M	42	0
Premanifest 2	33	M	43	0
Premanifest 3	35	M	45	4
Premanifest 4	32	M	41	0
Premanifest 5	29	M	42	0
Premanifest 6	26	M	42	0
Premanifest 7	55	M	38	0
Early manifest 1	47	F	45	14
Early manifest 2	60	F	39	6
Early manifest 3	58	F	43	34
Early manifest 4	58	F	39	5
Early manifest 5	46	F	46	32
Early manifest 6	58	M	41	18
Early manifest 7	50	F	42	10
Early manifest 8	43	M	44	10

further identification and removal of ocular-related artifacts.

2.3. Working memory task

Following our previous study (Semprini et al., 2020), we distinguished between three WM phases: memory update, maintenance and readout, based on different cognitive processes involved during the task, i.e. encoding of novel information, maintenance of that information when new stimuli arrive and finally readout of stored information.

In this study, we did not include the analysis of the badly performed trials, i.e. incorrectly recognized probe letters (false positive, FP, and false negative, FN), because their small number made it impossible to statistically validate the analysis of their related neural activity. We thus only focused on true positive (TP) trials, i.e. correctly recognized probe letter as matching the stimulus letter (button press), and true negative (TN) trials, i.e. correctly recognized probe letter as non-matching the stimulus letter (no button press).

We assessed task performance by collecting reaction time, defined as the delay between probe letter onset and button press for TP trials only, and accuracy, defined as $\frac{TP+TN}{TP+TN+FP+FN}$.

2.4. EEG processing and ERS/ERD analysis

For this analysis, we excluded one patient from HD group because of excessive movements during hdEEG recording and one subject from the control group because of technical problems during acquisition.

We followed the same procedure already described in (Semprini et al., 2020). Briefly, we chose a specific set of regions of interest (ROIs) in the brain, whose activation was found to be related to the n-back task (Mencarelli et al., 2019). Table 2 summarizes the observed ROIs.

We first preprocessed the EEG data by applying a notch filter centered at 50 Hz. Then, we detected channels with low signal to noise ratio and interpolated them by using information coming from the neighboring channels, as implemented in the FieldTrip toolbox (https://www.fieldtriptoolbox.org/). EEG signals were then band-pass filtered (1–80 Hz) with a FIR zero-phase distortion filter and down-sampled at 250 Hz. We removed biological artefacts using Independent Component Analysis (ICA) as described in (Mantini et al., 2008). We finally performed source reconstruction as in (Liu et al., 2017; Semprini et al., 2020), by means of the exact low-resolution brain electromagnetic tomography eLORETA algorithm, using both the artifacts-free hdEEG signals and a head model conductor, obtained with Simbio finite element method (FEM) implemented in FieldTrip starting from an MNI template, as in (Liu et al., 2017). We computed event related synchronization and desynchronization (ERS/ERD) of source reconstructed data filtered in different frequency bands and during different WM processing phases. Specifically, for each WM phase (update, maintenance and readout) we generated a spectrogram for the frequency range 1–80 Hz, at steps of 1 Hz, and with temporal resolution equal to 100 ms. The spectrograms were epoched, according to each specific condition (see below) and then averaged. Finally, we calculated ERS/ERD intensity as the power change of the signal in a specific time range with respect to a reference period (baseline), always set to the 500 ms preceding letter presentation as in (Hoy et al., 2016).

The observed frequency bands were θ (4–8 Hz), β (13–30 Hz), γ_{LOW} (30–50 Hz), and γ_{HIGH} (50–80 Hz) as in our previous study (Semprini et al., 2020). As in (Semprini et al., 2020), time ranges were set as follows: between 100 and 1000 ms post stimulus onset for update; between 1000 and 2000 ms post distractor onset for maintenance; and between 100 and 600 ms post stimulus onset for readout.

2.5. Statistical analysis

For behavioral data we run two RM-ANOVA, one for reaction time and one for accuracy, with TASK (2-back and 3-back) as within-subjects factors, and GROUP (HD and CTRL) as between-subjects factor.

For EEG data, RM-ANOVA was run to highlight differences between HD and CTRL groups on the mean ERS/ERD intensity, with TASK (2-back and 3-back) and PHASE (update, maintenance and readout) and TRIAL (TP, TN) as within-subjects factors, and GROUP (HD, CTRL) as between-subjects factor. This analysis was run separately for each ROI and for each frequency band. The significance level p was corrected for multiple comparisons according to the FDR procedure ($pFDR < 0.05$) (Benjamini and Hochberg, 1995). Brain oscillations interactions with disease burden (CAP) score were investigated by means of linear regression.

Statistical analysis was performed with SPSS 22.0. The significance level was set to $p < 0.05$ and to $pFDR < 0.05$ after correction for multiple comparison (Benjamini and Hochberg, 1995). Post-hoc analysis of significant interactions was performed by means of Fisher's least significant difference procedure.

Table 2
List of observed ROIs, areas they belong, and corresponding MNI coordinates.

Cluster	Areas	Side	X	Y	Z	Acronym
Medial frontal cortex	Medial frontal gyrus	R	2.19	19.92	44.69	MeFC
	Medial frontal gyrus	L				
Prefrontal Cortex	Dorsolateral prefrontal cortex	R	45.14	38.44	24.49	PFC-R
	Anterior prefrontal cortex					
Premotor cortex	Premotor area	R	31.93	9.21	55.85	PMC-R
Insula	Insular cortex	R	34.68	23.81	−3.85	InsCl-R
	Claustrum					
Posterior Parietal cortex	Superior parietal lobule	R	40.12	−50.39	45.26	PPC-R
	Inferior parietal lobule					
	Precuneus					
Cerebellum	Cerebellar Tonsil	R	32.83	−63.53	−33.84	CerT-R
Dorsolateral prefrontal cortex	Dorsolateral prefrontal cortex	L	−39.41	52.62	9.74	DLPFC-L
Frontal cortex	Premotor area	L	−45.07	8.71	30.67	FC-L
	Dorsolateral prefrontal cortex					
Premotor cortex	Premotor area	L	−27.12	4.54	52.5	PMC-L
Insula	Insular cortex	L	−32.58	22.31	−5.41	InsCl-L
	Claustrum					
Posterior Parietal cortex	Superior parietal lobule	L	−36.4	−49.09	45.35	PPC-L
	Inferior parietal lobule					
	Precuneus					
Fusiform cortex	Fusiform gyrus	L	−46.06	−63.51	−15.36	Fus-L
Cerebellum	Cerebellar Tonsil	L	−31.93	−64.21	−33.44	CerT-L
Cerebellum	Cerebellar Pyramis	L	−8.72	−78.15	−32.26	CerP-L

3. Results

3.1. Working memory performance

No significant difference was observed regarding reaction time data (Fig. 1) between groups (GROUP: $F_{1,28} = 0.35$, $p = 0.55$). Furthermore, no significant effect of TASK ($F_{1,28} = 3.18$, $p = 0.08$) or interaction TASK* GROUP ($F = 0.00$; $p = 0.98$) was found. This result is in line with our previous work, probably because all subject groups were prioritizing accuracy over timing (Hur et al., 2017).

On the contrary, accuracy analysis revealed a significant difference between HD and CTRL groups [GROUP ($F_{1,28} = 13.69$, $p = 0.001$)] where HD patients performed worse than CTRL. Furthermore, a significant effect of TASK ($F_{1,28} = 37.59$, $p < 0.001$), was also found, and with accuracy of 2-back task higher than during 3-back (Fig. 1).

3.2. ERS/ERD analysis

Related to oscillations in the different bands, the effect of PHASE (Table S1) was significant for θ band in all areas of the working memory network (always $p < 0.05$) except DLPFC-L. Confirming our previous findings, we observed increased θ oscillation in update and readout with respect to maintenance. We also found a significant GROUP*PHASE interaction ($p < 0.03$) for all the analysed areas except PFC-R, FC-L, InsCl_L and CerP_L (Fig. 2 and Table S2 Supplementary Materials). HD had smaller θ oscillations with respect to controls in the update and readout phases (post hoc analysis always $p < 0.02$).

For β band, in the majority of the WM network (except a few areas, i.e., PFC-R, DLFPC-L, InsCl-L) and InsCl_R and FC_L, which displayed a trend towards significance, we observed increased oscillations during maintenance with respect to update and readout, confirming our previous findings (Fig. 3 and effect of PHASE, Table S3). No significant effect of GROUP or interaction GROUP*PHASE was found.

For γ oscillations, we observed only a focal increase in γ_{HIGH} oscillations during readout with respect to maintenance and update in CerT-L, CerP-L and no effect of PHASE for γ_{LOW}. No significant effect of GROUP or interaction GROUP*PHASE was found.

3.3. Correlation with disease burden score

CAP score showed a significant and inverse correlation during maintenance in 2-back task with γ_{HIGH} activity in CerT-L (rho = -0.77p = 0.043), CerP-L (rho = -0.78p = 0.043) and FUS-L (rho = -0.71p = 0.048). No significant correlation was found between CAP score and θ (always $p > 0.05$) and β (always $p > 0.05$) band modulations during WM task.

4. Discussion

The aim of this study was to test whether hdEEG coupled to source localization allows for the identification of neuronal oscillations in specific frequency bands during the different phases of working memory (update, maintenance, readout) in the n-back task in a group of pre-manifest and very early manifest HD patients.

First, confirming our previous results, we found specific spectral signatures associated with updating of memory information, WM maintenance and readout, with relatively high spatial resolution. Then, related to differences between HD patients and controls the main result was linked to reduced θ oscillations in HD with respect to controls in almost all the areas of the WM network during the update and readout phases. Furthermore, accuracy was reduced in both 2-back and 3-back tasks in HD with respect to controls. Finally, in HD patients, we found significant correlations between disease burden score and γ oscillations in the maintenance phase.

Reduced θ oscillations in the update and readout phase were detectable in most of the areas of the WM network in patients with HD with respect to controls. Synchronization in the θ band in the areas of the WM network following stimulus presentation is consistent with long-range coordination of neuronal activity within this network (Von Stein and Sarnthein, 2000). Indeed, low-frequency oscillations are thought to synchronize neural networks by temporally coordinating excitability in different brain regions. This mechanism, known as "communication through coherence," permits integration of distributed brain areas required to perform complex tasks (Fries, 2015). In accordance with our "dynamic" finding of reduced θ power increase during update and readout phases of WM, reduced θ power has been also described in HD patients from early to late stages of the disease in resting EEG (Painold et al., 2011). Painold and co-workers (Painold et al., 2011) found decreased θ power all over the cortex with frontal, temporal, parietal, limbic and sub-lobar areas, with nearly all possible voxels involved (80%), already in very-early manifest HD patients. The ubiquitous decrease in θ was hypothesized to reflect an accumulation of cortical structural impairment together with the alterations of the basal ganglia. (Rosas et al., 2008; Rosas et al., 2003). Indeed, whether altered θ oscillations in HD reflect exclusively an accumulation of cortical structural impairment or an imbalance between intracortical inhibitory and excitatory connections because of basal ganglia-thalamo-cortical loop dysfunction (Abbruzzese et al., 1997) is still under discussion. Recently, Hawellek and co-workers reported that patients with HD treated with the huntingtin-lowering antisense oligonucleotide tominersen exhibited increased resting state EEG power in the theta/alpha frequency range (Hawellek et al., n.d.). The underlying mechanisms of the observed changes are unknown but may reflect neural plasticity as a consequence of the molecular pathways impacted by tominersen treatment,

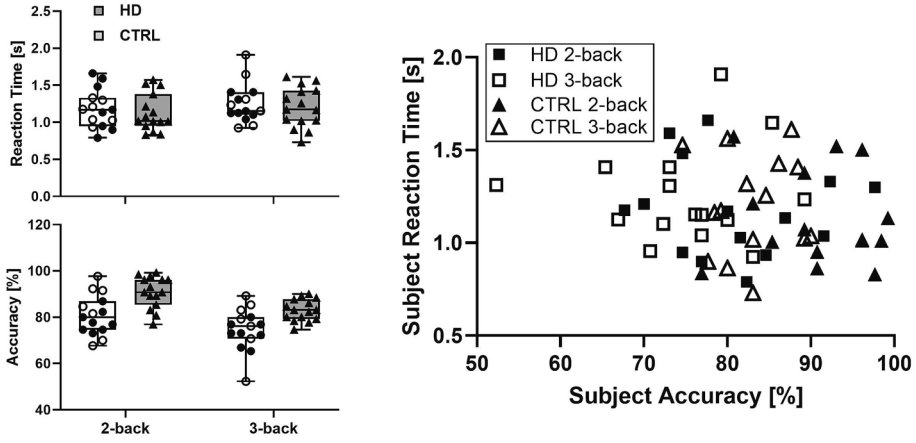

Fig. 1. Performance at the n-back task. In the top left panel, we show average reaction times obtained by HD patients (pre-HD, white circles; early-HD black circles) and control subjects (CTRL, black triangles) during the 2-back and 3-back task. In the bottom left panel average accuracy obtained HD patients (pre-HD, white circles; early-HD black circles) and control subjects (CTRL, black triangles) during the 2-back and 3-back task is shown. For both single subjects' scores are reported with boxplots describing the median value, 25th and 75th percentiles, whiskers (min to max). Right panel, mean accuracy vs mean reaction times of single subjects of the HD group (squares) and control group (triangles) in the 2-back and 3-back (respectively black and white) task.

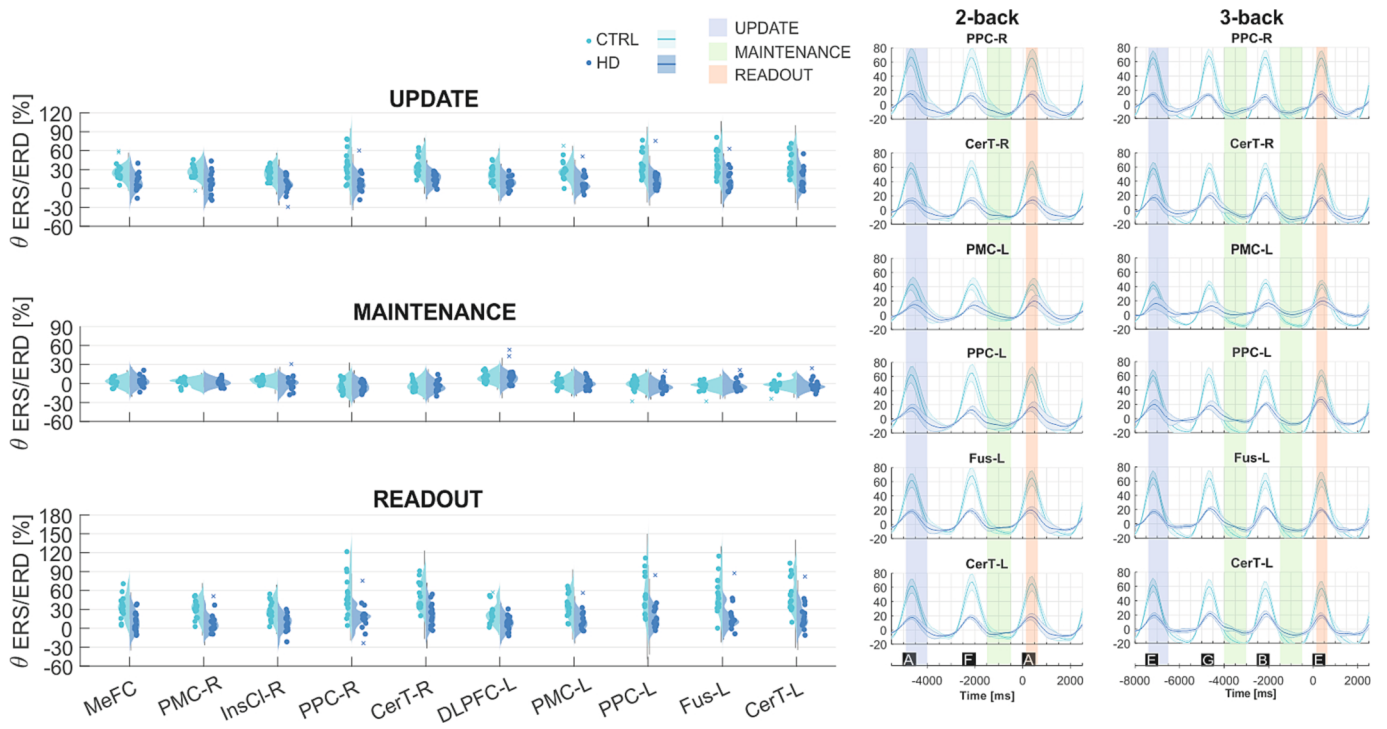

Fig. 2. Effect of GROUP*PHASE in the θ band. Mean data across 2-back and 3-back tasks are shown since no effect was found for TASK or GROUP*PHASE*TASK interaction. On the left, panel A, we report violin plots of ERS/ERD variation in the θ band of HD patients (HD, blue) and healthy controls (CTRL, light blue) during update (top), maintenance (middle) and readout (bottom). Dots represent single subject data. On the right, panel B, we report temporal evolution of band power in the θ band of HD patients (HD, blue) and healthy controls (CTRL, light blue) during the 2-back and the 3-back task for example areas, PPC-R, CerT-R, PM-L, PPC-L, Fus-L and CerT-L.

supporting the hypothesis that reduction of θ oscillations may represent the neurophysiological correlate of a loss of brain activity in line with synaptic dysfunction and progressive neuronal loss in HD (Bertoglio et al., 2022; Delva et al., 2022).

In a recent study, "dynamic" reduction of θ power has been also described in HD mutation carriers following transcranial magnetic stimulation of the primary motor cortex (M1) (Casula et al., 2018). The amplitude of the third peak of the transcranial evoked potential, evoked from M1, about 150 and 250 ms after the TMS pulse, was reduced in HD mutation carriers and time/frequency domain analyses revealed that the lower TMS-evoked response in HD resulted from reduced synchronization of θ and αbands. Overall, these data suggest that impairments of synchronization in the θ band could be a physiological basis for some key clinical features of HD.

Interestingly, even if there were no differences in γ oscillations between HD and CTRL during update, maintenance and readout of WM, γ_{HIGH} oscillations during maintenance in cerebellum and FUS-L inversely correlated with disease burden score. Differently from θ oscillations, higher frequencies, and particularly γ oscillations, are linked to intra-cortical synchronization (Singer, 2009). Gamma oscillations might represent a rhythmic synaptic inhibition mediated by parvalbumin-expressing inhibitory interneurons, that are the most common type of GABAergic neurons within the brain, and the interconnected pyramidal neurons (Sohal, 2016). Experimental studies showed that disrupted GABAergic circuits underlie HD pathogenesis and that restoring GABAergic inhibition rescues memory deficits in a HD mouse model (Dargaei et al., 2018). Our result suggests that γ_{HIGH} oscillations in the maintenance phase in cerebellum and left fusiform gyrus are possibly linked to HD pathology: the higher the disease burden score, the more reduced the oscillations. It has been shown that activity in the cerebellum is reduced in pre-HD and symptomatic HD, relative to controls, already in a WM task of low complexity, as 1-back task, suggesting a functional brain reorganization also in subcortical regions in both pre-HD and symptomatic HD groups (Georgiou-Karistianis et al., 2013).

Finally, it is noteworthy to comment that because of the continuous nature of the behavioral paradigm, update and read-out phases share a portion of the time window used for calculation of their respective ERS/ERD signals, which may affect our results. However, the different modulation of γ oscillations found for these phases, indicates the reliability of the analysis for the n-back task. Further investigations of the different phases involved in the working memory process should make use of different tasks, which allow to clearly discern phases of working memory, such as the 'delayed-match-to-sample' task (Daniel et al., 2016).

The main limitation of the study is related to the sample size. Indeed, these are preliminary results obtained in a well-selected small sample of pre-manifest HD gene carriers and early manifest HD patients; however, our sample size is normally distributed, and it number was similar to the one proposed by other studies (Hoy et al., 2013; Van Der Hiele et al., 2007).

5. Conclusions

Here we showed that pre-manifest HD gene carriers and early manifest HD patients already present phase specific modulation in different EEG bands during n-back task, even if oscillations are globally decreased in HD. These results provide novel information on pathophysiological mechanisms at the basis of WM dysfunction in HD and pave the road to the use of non-invasive brain stimulation to improve WM performance in HD. Non-invasive brain stimulation is a popular tool, often associated with conventional therapy, able to improve brain functions, depending on target brain areas. Lately, it has been also used to enhance working memory ability (Hoy et al., 2015). Specifically, transcranial Alternating Current Stimulation (tACS) in the EEG range (conventionally: 0.1–80 Hz) is used to potentiate WM and processing speed in subjects with impaired cognitive abilities (Shanbhag et al.,

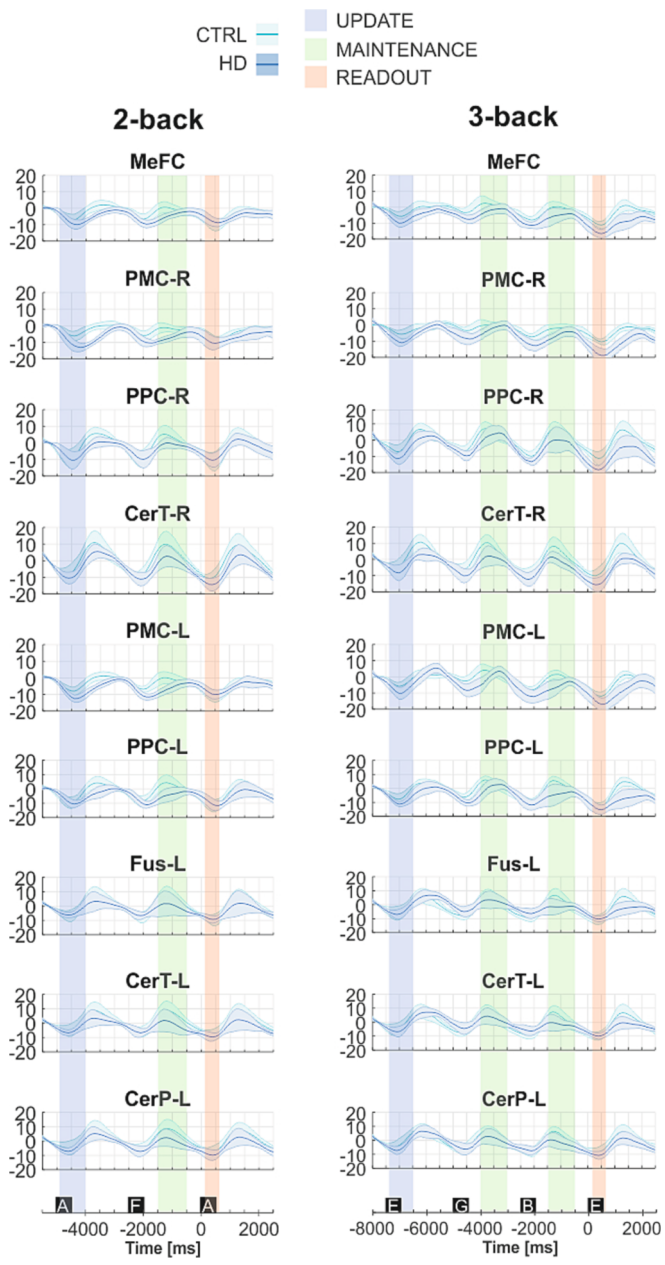

Fig. 3. Effect of PHASE in the β band. We report temporal evolution of band power in the β band of HD patients (HD, blue) and healthy controls (CTRL, light blue) during the 2-back and the 3-back task during update (top), maintenance (middle) and readout (bottom).

2019). Identifying key areas and proper timings for neuromodulation delivery in HD patients is instrumental to provide effective treatment and to correct abnormal brain oscillation. Finally, measures of synchronization during a WM task could be valuable as a functional readout for the evaluation of treatments in HD.

CRediT authorship contribution statement

Gaia Bonassi: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Marianna Semprini:** Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Paola Mandich:** Data curation, Writing – review & editing. **Lucia Trevisan:** Data curation, Writing – review & editing. **Roberta Marchese:** Data curation, Writing – review & editing. **Giovanna Lagravinese:** Data curation, Writing – review & editing. **Federico Barban:** Data curation, Formal analysis, Writing – review & editing. **Elisa Pelosin:** Conceptualization, Writing – review & editing. **Michela Chiappalone:** Conceptualization, Writing – review & editing. **Dante Mantini:** Conceptualization, Writing – review & editing. **Laura Avanzino:** Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

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

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brainres.2023.148540.

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