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Auditory mismatch negativity in pre-manifest and manifest Huntington's disease

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HIGHLIGHTS

- Mismatch negativity paradigm (MMN) showed compromised early auditory and pre-attentive processes in manifest Huntington Disease (HD).
- In premanifest HD, MMN amplitude was similar to manifest HD, but theta coherence was increased compared to manifest HD and controls.
- Initial decline of Mismatch Negativity, together with changes in theta power coherence, could characterize HD in the pre-manifest phase.

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ABSTRACT

Aim: The aim of this study was to investigate the characteristics of the electrophysiological brain response elicited in a passive acoustic oddball paradigm, i.e. mismatch negativity (MMN), in patients with Huntington's disease (HD) in the premanifest (pHD) and manifest (mHD) phases. In this regard, we correlated the results of event-related potentials (ERP) with disease characteristics.
Methods: This was an observational cross-sectional MMN study. In addition to the MMN recording of the passive oddball task, all subjects with first-degree inheritance for HD underwent genetic testing for mutant HTT, the Huntington's Disease Rating Scale, the Total Functional Capacity Scale, the Problem Behaviors Assessment short form, and the Mini-Mental State Examination.
Results: We found that global field power (GFP) was reduced in the MMN time window in mHD patients compared to pHD and normal controls (NC). In the pHD group, MMN amplitude was only slightly and not significantly increased compared to mHD, while pHD patients showed increased theta coherence between trials compared to mHD. In the entire sample of HD gene carriers, the main MMN traits were not correlated with motor performance, cognitive impairment and functional disability.
Conclusion: These results suggest an initial and subtle deterioration of pre-attentive mechanisms in the presymptomatic phase of HD, with an increasing phase shift in the MMN time frame. This result could indicate initial functional changes with a possible compensatory effect.
Significance: An initial and slight decrease in MMN associated with increased phase coherence in the corresponding EEG frequencies could indicate an early functional involvement of pre-attentive resources that could precede the clinical expression of HD.

Abbreviations: HD, Huntington's Disease; pHD, Huntington's Disease Group in pre-manifest stage; mHD, Huntington's Disease Group in manifest stage; NC, Healthy Control Group; TFC, Total Functional Capacity Scale; UHDRS, Huntington's Disease Rating Scale; PBA, Problem Behaviors Assessment short form; EEG, Electroencephalographic; MMN, Mismatch Negativity; ERP, event-related potential; EOG, electrooculogram; ICA, Independent Component Analysis; ANOVAs, Analyses of Variance; NMDA, N-methyl-D-aspartate receptors.

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1. Introduction

1.1. Phenotypic expression of Huntington's disease and main pathophysiological basis

Huntington's disease (HD) is a progressive neurodegenerative disorder that leads to severe motor, psychiatric and cognitive symptoms. HD is caused by autosomal dominant inheritance of an expanded CAG repeat within an exon of the Huntington's disease gene HTT on chromosome 4 (Novak et al., 2011). Genetic testing allows the identification of the causative gene (mutated huntingtin, HTT) and confirms the diagnosis and the risk of phenotypic manifestations. Huntington's disease causes widespread brain pathology with progressive dysfunction and death of neurons in corticostriatal circuits. As the disease progresses, the neurodegenerative changes also extend to the cortical gray matter areas (Kassubek et al, 2004; Rosas et al, 2002). Cortical atrophy is found in both the premanifest (pHD) and manifest stages of HD (mHD), with increasing cortical thinning occurring as disease severity progresses (Rosas et al, 2008; Tabrizi et al, 2009).

1.2. Presymptomatic-neurophysiological-biomarkers

Neuropsychological studies indicate that subtle motor (Blekher et al, 2004; De Boo et al, 1997; Kirkwood et al, 1999; Kirkwood et al, 2000; Paulsen et al, 2008; Siemers et al, 1996; Smith et al, 2000; Snowden et al, 2002), cognitive (Diamond et al, 1992; Kirkwood et al, 2000; Paulsen, et al2001) and psychiatric signs and/or symptoms (Berrios et al, 2002; Berrios et al, 2001; Close Kirkwood et al, 2002; Hahn-Barma et al, 1998; Paulsen et al, 2001) are present years before clinical diagnosis. Therefore, clinical and instrumental assessment of the presymptomatic stage may provide potential biomarkers and improve knowledge of the neural circuits affected by mutant HTT in the presymptomatic phase. The clinical relevance of electrophysiological testing in HD patients is well described in the literature (Lefaucheur et al, 2002). The most common electroencephalographic (EEG) abnormality described in HD is a reduction in amplitude or suppression of alpha activity (Bellotti et al, 2004; Bylsma et al, 1994; de Tommaso et al, 2003; Streletz et al, 1990). In mHD and pHD, an association between abnormal synchronization of the main electroencephalography bands and aspects of cognitive decline has been found (Delussi et al, 2020). Abnormal processing of sensory stimuli has been described in mHD and even in pHD, with increased latency and decreased amplitude in somatosensory, nociceptive, visual and auditory evoked responses (Mayer et al, 2014). This phenomenon appears to be associated with a general defect in the initial phase of stimulus detection and cortical and subcortical processing (Croft et al, 2014). These neurophysiological aspects of Huntington's disease may be the cause of the poor reactive behavior and apathy that characterize the phenotypic expression of this complex disorder.

1.3. Mismatch negativity-previous results in HD

Event-related potential (ERP) mismatch negativity (MMN) reflects the pre-attentive ability to select and filter relevant sensory information in a non-pre-informed cognitive set (Naatanen et al, 2011). EEG MMN is typically observed in auditory tasks where a set of frequent standard stimuli is interspersed with (less frequent) deviant stimuli (de Tommaso et al, 2020). The MMN is automatically generated when there is a discrepancy between the neural model of the physical features of the standard stimulus and the deviant stimulus, which occurs approximately 100–250 ms after stimulus variation onset (Garrido et al., 2008). It is generally determined by subtracting the response related to the standard stimulus from the response related to the deviant stimulus. The negative difference is evident at the frontal recording sites (O'Reilly et al, 2021). The reduction in MMN amplitude has been proposed as an indicator of deficient N-methyl-d-aspartate (NMDA) receptor function, which impairs memory trace formation and thus cognition in various clinical conditions (Dhawan et al, 2010). In a previous study using the EEG-MMN paradigm, in which participants played an active role in detecting stimulus deviations, HD patients showed a stronger MMN response than healthy subjects (Beste et al., 2008). Similarly, intact performance in recognizing deviant stimuli in an active oddball task design has also been described in HD (de Tommaso et al, 2017). However, in another study using a passive oddball paradigm in manifest HD patients and control subjects, reduced waveform amplitude and prolonged peak latency of magnetic mismatch responses were found (Chen et al, 2014).

1.4. Aims of the study

In this study, we apply a passive MMN paradigm in premanifest and manifest HD patients and in a group of healthy control participants to clarify whether MMN is preserved in HD. Our hypothesis is that mHD may confirm a deficit in preattentive processing, with a possible initial dysfunction in the presymptomatic carriers. To this end, we also investigated stimulus-related EEG oscillatory properties and phase coherence, as these features may shed light on a possible preattentive processing disorder in manifest and premanifest HD (Ko et al., 2012).

2. Methods

2.1. Study design and subjects

This was an observational cross-sectional study with EEG recording. It was conducted between January 2019 and January 2021 at the Apulian Reference Center for Huntington's disease. We enrolled 45 non-medicated patients who came to our HD center for the first time for admission to the day clinic for genetic and clinical evaluation and 39 healthy control participants. The inclusion criteria for patients were age $\geq$ 18 years, no previous treatment and first-degree heredity for HD. In contrast, exclusion criteria included the presence of severe chorea movements that could interfere with EEG recording, previous or current medication use and the concurrent presence of other neurological or psychiatric disorders. The latter criterion also applied to the control participants. Eight patients did not fulfill the criteria. Thus, the final sample consisted of a total of 29 mHD (13 women; age: M = 51; range 18–75), 14 pHD (11 women; age: M = 42; range 20–63) and 39C (16 women; age: M = 36; range 18–73) (Fig. 1). Each participant underwent a daily clinical examination as described in Delussi et al. (Delussi et al., 2020).

The Ethics Committee of the University Hospital of Bari approved the study and each subject signed a consent form.

2.2. Neurological and psychiatric assessment

We performed the Diagnostic Confidence Level (DCL) of the Total Motor Score (TMS) as part of the Huntington's Disease Rating Scale (UHDRS) (Unified Huntington's Disease Rating Scale; 1996, Hogarth, 2005) and the Total Functional Capacity Scale (TFC) (Shoulson, 1981) to assess the presence of motor manifestations clinically interpreted as "clear signs of Huntington's disease" and

the Problem Behaviors Assessment short form (PBA-s) (Kingma et al, 2008) for psychiatric assessment. The Mini-Mental State Examination (MMSE) was also used (Folstein, 1975).

2.3. Genetic investigation

Characterization of the CAG triplet repeat of the HTT gene was performed on DNA extracted from peripheral blood lymphocytes of potential carriers by detecting the expansion of CAG trait 40 in one allele of the IT-15 gene (Novak et al, 2011).

2.4. Electroencephalographic examination

The EEG recording was performed with the subject positioned in a softly lit and soundproofed room with an ambient temperature of 21–23∘C, in an awake and relaxed state, in a sitting position. The EEG recordings were obtained by a waveguard EEG cup with Ag/AgCl surface electrodes on the scalp, according to an extension of the International System 10–20 (Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, Oz, O2, FC2, FC1, CP1, CP2, PO3, PO4, FC6, FC5, CP5, CP6, AF7, AF3, AFz, AF4, AF8, F5, F1, F2, F6, FT7, FC3, FCz, FC4, FT8, C5, C1, C2, C6, TP7, CP3, CPz, CP4, TP8, P5, P1, P2, P6, PO7, POz, PO8). All these electrodes were prewired on a standard headset, with a common reference electrode positioned on the nasion (lead in common reference inactive), two electrodes were placed on the right and left lower eyelid, respectively to detect eye movements (electro-oculographic channel - EOG) and an earth electrode placed on the back of the hand. The electrode impedances were kept below 5 kΩ and a sampling frequency of 256 Hz was used for the acquisition. The EEG signals were amplified, filtered, and saved on a biopotential analyzer (Micromed System Plus, Micromed, Mogliano Veneto, Italy).

2.5. EEG MMN paradigm

The auditory task used to elicit the EEG-MMN was a passive oddball task with stimuli that varied in frequency. A sequence of 1000 pure tones was presented to both ears via headphones while participants read a local newspaper. The standard stimuli had a frequency of 500 Hz and a duration of 75 ms, while the deviant stimuli had a frequency of 1500 Hz and a duration of 75 ms. The standard:deviant ratio was 9:1. Deviant and standard stimuli were pseudo-randomly shuffled. Participants were instructed to ignore the auditory cues and focus on the newspaper. The task lasted approximately 20 minutes.

2.6. EEG data pre-processing

Offline, the EEG signal was processed with the MATLAB-based toolbox Brainstorm (Tadel, 2011). A bandpass filter with cutoff frequencies of 0.1 Hz and 30 Hz (Fuentemilla et al, 2008; Luck et al, 2014) was applied to remove slow EEG drifts and high frequencies. Since the MMN is strong in the EEG over the medial electrodes, preprocessing of the data was limited to 25 electrodes for the detection and correction of artifacts with independent component analysis (ICA): Fz, F1/2, F3/4, FCz, FC1/2, FC3/4, Cz, C1/2, C3/4, CPz, CP1/2, CP3/4, Pz, P1/2, P3/4. This procedure ensured high precision in the calculation of independent components related to artifacts that could significantly distort the signal of interest and in the correction of relevant ocular or muscular artifacts (Jiang et al., 2019). The signal was then visually inspected for remaining artifacts and parts of the signal with artifacts were discarded.

2.7. EEG MMN signal processing

Epochs were created for standard and deviant stimuli from 200 ms before stimulus onset to 800 ms after stimulus onset. This longer duration was necessary to attenuate edge artifacts in the time–frequency analysis. The interval of 200 ms before stimulus onset served as a baseline. The median number of artifact-free epochs of deviant stimuli was 94 (range 86–100) in pHD, 85 (range 61–100) in mHD, and 91 (range 68–100) in NC. A subset of artifact-free standard epochs was selected with a numerosity equal to that of artifact-free deviant epochs, evenly distributed throughout the sequence of stimuli. To calculate the MMN, the average activity of this subset of standard stimuli was subtracted from the average activity of the deviant stimuli. This ensured that the same number of artifact-free trials were computed for both the standard and deviant stimuli. After averaging, ERPs were normalized to z-scores based on the 200 ms pre-stimulus interval. First, the maximum amplitude of global field power (GFP) within the 150–225 ms was extracted to assess the overall amplitude of brain electrical activity in the MMN time window. Subsequently, the analysis focused on the averaged amplitude and latencies and the corresponding latencies of the negative ERP peak between 150 and 225 ms calculated in a region of interest from three frontocentral electrodes (Fz, FCz and Cz), which are standard locations for analyzing the MMN in response to auditory stimuli. Topographic analysis of statistical differences between groups was performed on 25 scalp electrodes. Latencies were calculated at the maximum amplitude of GFP and ERP. In the time–frequency analyses, the signal was processed with a series of complex Morlet wavelets (Cohen, 2014). The complex sine waves ranged from 1 Hz to 30 Hz, while the Gaussian taper increased as a function of frequency from 4 to 10 cycles. The time–frequency power was calculated as the average power of the complex value functions and converted to decibels (dB) to obtain the signal changes compared to the baseline (from −200 to −40 ms). The phase coherence between the trials was the mean angle of the complex value functions.The MMN is associated with theta activity (Fuentemilla, 2008). Therefore, only the theta band activity between 4 and 9 Hz was considered in the power and ITPC analyses, looking for the largest positive peak in the 0–300 ms time window of the Fz, FCz and Cz signal. The main effect of group (mHD, pHD and NC) was analyzed in analyses of variance (ANOVAs) that also included gender as an additional between-participant factor and age as a covariate to account for demographic differences between groups. The significance level of the ANOVAs was $\alpha = 0.05$, while α was adjusted to 0.016 for all follow-up tests according to Bonferroni. Correlations of MMN parameters (i.e. ERP amplitude, theta power and theta inter-trial phase coherence) with scores in neurological, psychiatric and genetic assessments in the two HD groups were performed to identify significant associations between neurophysiological activity and clinical parameters. The Pearson correlation test was used for this purpose.

3. Results

3.1. Demographic and clinical data

The data of one participant in the mHD group were excluded because he had MMN amplitude values of more than 1.5 interquartile differences compared to the other participants in his group. Significant differences were observed between the three groups in terms of both mean age and sex distribution, $p < 0.01$ (see Fig. 1). The main clinical characteristics of the HD patients are listed in Table 1.

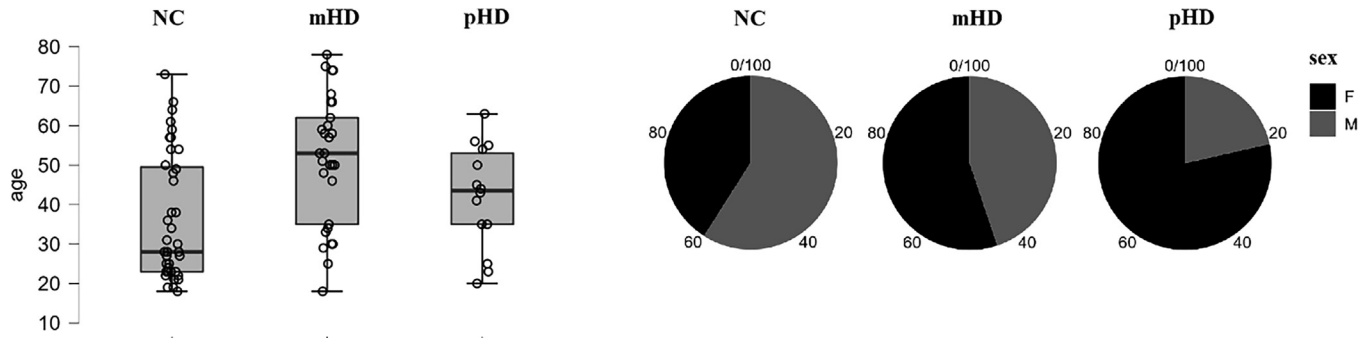

Fig. 1. Representation of age and sex distributions in the three groups. NC: Normal Controls; pHD: pre-manifests Huntington's disease patients; mHD: manifest Huntington's disease patients.

MMN GFP and ERP amplitude. The analysis of the MMN GFP peak amplitude resulting from the subtraction of the standard from the deviant activity at the Fz, Fcz and Cz electrodes (i.e. the MMN, see Fig. 2) revealed a significant effect of group, F (2,74) = 4.09, p =.021, ηp2 = 0.100. This main effect showed that the MMN amplitude was significantly smaller at mHD than at NC, F(1,62) = 6.95, p =.011, ηp2 = 0.101, with no significant difference between pHD and NC, F(1,48) = 0.40, p =.530, ηp2 = 0.008, and between pHD and mHD, F(1,37) = 3.35, p =.075, ηp2 = 0.083.

Analysis of the maximum amplitude of the MMN-ERP in the fronto-central electrodes on the midline revealed a significant main effect of group, F (2,74) = 3.13, p =.050, ηp2 = 0.078. The main effect of group showed that although there was no significant difference in contrast between NC and pHD, F(1,48) = 0.30, p =.588, ηp2 = 0.006, MMN amplitude tended to be lower for mHD than for NC, F(1,37) = 5.04, p =.031, ηp2 = 0.120, and for mHD than for pHD, F(1,62) = 3.26, p =.076, ηp2 = 0.219. However, these two effects were not significant after α-correction for multiple comparisons.

3.2. Topographic analysis

When looking at the 25 scalp electrodes, we observed a significant reduction in MMN amplitude in the mHD group compared to the healthy subjects at the fronto-central electrodes. The mHD patients showed a reduction in MMN amplitude in the right frontal region compared to the pHD group (Fig. 2).

3.3. Time frequency power and inter-trial phase coherence

The MMN analyses in the time–frequency (see Fig. 3) domain showed significant effects of Group for both theta power, F (2,74) = 6.01, p =.004, η_p^2 = 0.140, and theta inter-trial phase coherence, F(2,74) = 4.14, p =.020, η_p^2 = 0.100. On the one hand, the main effect of Group for theta power indicated that mHD showed smaller theta power than NC, F(1,62) = 9.26, p =.003, η_p^2 = 0.130, and pHD, even though the difference showed only a trend toward significance, F(1,37) = 3.28, p =.078, η_p^2 = 0.082; the difference was not significant between NC and pHD F < 1. On the other hand, the main effect of Group in theta inter-trial phase coherence reflected larger phase synchronization in pHD compared to mHD, F(1,37) = 7.85, p =.008, η_p^2 = 0.175, but no difference between NC and pHD, F(1,48) = 2.08, p =.156, η_p^2 = 0.042, and between NC and mHD, F(1,62) = 1.00, p =.319, η_p^2 = 0.016.

3.4. MMN latency

Between-trial analyses of MMN ERP peak latencies, theta power, and theta phase coherence revealed no significant effects. Interestingly, however, the average latency of ERP MMN amplitude (186 ms) was significantly slower than the latency of theta power (150 ms) and theta intertrial phase coherence (134 ms). This difference in latency suggests that in the present experiment, the modulations of brain activity in the time–frequency domain occurred earlier than the commonly reported time window, likely affecting the earlier -P1-related potentials. (Supplementary Table 1).

3.5. Correlation between MMN and clinical data

None of the correlations between the MMN parameters (i.e. ERP amplitude, theta power and theta intertrial phase coherence) and the scores for neurological, psychiatric and genetic assessments were significant.

4. Discussion

4.1. Main findings

This was an observational cross-sectional study of the EEG MMN ERPs in presymptomatic and symptomatic HD gene carriers and healthy controls. Our aim was to identify pathological EEG candidate biomarkers potentially linked to genetic, motor, cognitive and behavioral features for early diagnosis and detection of disease progression. In a standard passive auditory MMN protocol, we found reduced MMN amplitude in the manifest state compared to control subjects, at least at the frontal electrodes. Phase coherence of theta rhythms was increased in pHD compared to mHD and NC. In pHD, MMN amplitude was not significantly different from mHD patients. We found no significant interaction between MMN characteristics and disease severity scores.

4.2. Previous MMN findings in HD

The MMN is described in the literature as an index of mental performance in psychiatric and neurological disorders (Naatanen et al, 2011). Auditory MMN originates in a temporofrontal network responsible for the automatic detection of auditory changes (Alain et al, 1998; Naatanen et al, 2011). Beste et al. conducted an auditory oddball paradigm in which participants had to actively respond to the detection and discrimination of two different target stimuli and found that MMN, P3a and the reorienting response showed increased amplitude in the advanced stage of HD (Beste et al., 2008). These results could not be replicated in subsequent prospective studies. An experiment on the magnetic counterpart of MMN, using a standard passive protocol, found impaired automatic attentional shifting (Cheng et al., 2014) in the P3 response in HD patients, where a progressive ERP amplitude reduction was found instead (Hart et al., 2015). The authors described reduced

Table 1
Demographic data for the three groups and scores in the neurological, clinical, cognitive, and genetic assessments in manifest (mHD) and premanifest (pHD) Huntington disease patients. Results of one way ANOVA test and chi-squared test are reported.

	NC	mHD	pHD	
AgeSex	36.2 (16.0)	52.6 (15.4)	42.1 (13.2)	$F(2,78) = 9.25$, $p < .001$
(F-M)	16–23	13–1635.4	11–32.4	$X^2(2, N = 82) = 6.0$, $p = .047$
UHDRS-TMS		(18.6)	(1.8)	$F(1,41) = 43.56$, $p < .001$
UHDRS-TFC		8.5 (3.3)	12.3 (2.0)	$F(1,41) = 14.94$, $p < .001$
MMSE		22.5 (4.4)	28.7 (3.6)	$F(1,41) = 19.36$, $p < .001$
CAG triplets		43.0 (6.0)	42.3 (3.1)	$F(1,41) = 0.19$, $p = .665$
Illness duration (years)		4.0 (2.8)	0	
PBA				
Depression		5.0 (4.4)	2.8 (3.0)	$F(1,37) = 2.67$, $p = .110$
Irritability		2.8 (4.0)	1.9 (5.0)	$F(1,37) = 0.36$, $p = .554$
Psychosis		1.1 (2.0)	1.7 (2.7)	$F(1,37) = 0.58$, $p = .450$
Apathy		1.7 (2.3)	0.4 (1.1)	$F(1,37) = 3.52$, $p = .069$
Executive functioning		1.3 (2.1)	0.3 (1.1)	$F(1,37) = 2.58$, $p = .117$

activation of bilateral frontal mismatch responses in the patients and linked this observation to a deficit in involuntary attentional switching in HD.

4.3. Present findings on MMN in mHD and pHD

Our results are essentially in agreement with the results of magnetic MMN (Cheng et al, 2014). We did not observe an increase in MMN in manifest HD, but a significant decrease compared to controls. Non-symptomatic carriers showed normal MMN amplitude and GFP, but the fact that we could not find a clear difference from the manifest HD group may have a significance for the within- group variability in the initial attenuation of the acoustic pre-attentive process. We investigated the phase coherence of MMN between trials, which is a sign of phase switching and power modulation at theta frequency that is enhanced in the context of attentional shift to deviant stimuli, as a sign of cortical activation (Ko et al., 2012). In studies of schizophrenia, MMN amplitude and ITPC appeared to be only weakly correlated, leading the authors to hypothesize that they may be responsible for dissociable pathophysiological processes (Hua et al., 2023). Changes in the oscillatory properties of the cortical regions responsible for the pre-attentional shifts could be a first sign of cognitive dysfunction characterizing the preclinical phase of HD. Interestingly, the amplitude and phase coherence of the theta rhythm tended to begin before the averaged negative response, implicating earlier auditory cortical processing. Thus, dysfunction of cortical oscillatory properties could occur in the early phases of preattentive phenomena in the premanifest stage of HD. In addition to the bilateral sources of the MMN located near the primary auditory cortex, there is also a frontal generator involving mainly the right hemisphere (Giard et al, 1990). We did not perform a source analysis of the auditory ERP, but the topographic map indicated the central right frontal electrodes as those mainly involved in signal amplitude reduction in mHD patients compared to controls. The MMN abnormalities are thought to reflect deficient function of NMDA receptors involved in cognitive performance such as memory trace and shifting attention. In the early stage of Huntington's disease, high NMDA reactivity could lead to increased intracellular calcium loading and catabolic enzyme activity, triggering a cascade of events that precede neuronal dysfunction (Fan et al., 2006). From this perspective, the increase in intertrial phase coherence can be interpreted as a sign of NMDA receptor hyperfunction, which could interact with the initial toxic effect of mutant huntingtin in the degenerative process. The primary dysfunction in the striatal-cortical connections with the loss of function of early sensory and especially auditory processing could promote compensation based on NMDA receptor hyperactivation, which in turn could favor the excitotoxic phenomenon with further neuronal stress and deterioration.

4.4. Lack of correlation between MMN abnormalities and clinical features

We observed that the reduction in MMN amplitude and phase coherence was not related to the motor, functional and cognitive performances of the totality of HD gene carriers. Our pHD subjects showed no clear initial cognitive or behavioral abnormalities, at least in our tests. However, a more detailed cognitive examination, in which attentional capacities are examined in depth, could reveal subtle deficits that may correspond to MMN traits (Horta-Barba et al, 2023). We also observed that MMN amplitude and phase coherence were not related to signs of psychosis as measured by PBA-s. In a more recent study (Valt et al., 2022), MMN changes appeared as a common feature in psychotic disorders. These findings, which remain to be confirmed in larger HD series and in other neurodegenerative disorders characterized by psychosis, tentatively suggest that MMN reduction is not a feature of psychosis in HD gene carriers.

4.5. Study limitation

Analogous to most monocentric rare disease studies, our case series was small and only indicative of a potential value of MMN as a biomarker for early onset and progression of Huntington's disease, which needs to be determined in prospective multicenter studies. Furthermore, our participants were generally older adults, especially in the HD patient groups. Since MMN decreases with age (Naeaetaenen et al., 2011), it is possible that potential MMN reductions in the mHD group were statistically attenuated by the covariate age. Furthermore, a more detailed cognitive assessment might allow to find a correlation between preclinical and clinical attention deficits and MMN changes in amplitude and phase coherence.

4.6. Conclusions

To our knowledge, this is the first EEG MMN study in pHD and mHD crossed with genetic, motor, cognitive and behavioral traits. The results suggest that increased MMN phase coherence between trials while maintaining MMN amplitude may be an indicator of a presymptomatic phase in which the compensatory phenomena are active. However, further longitudinal studies are needed to confirm that the decrease in MMN amplitude is consistent with impending clinical manifestation without a marked worsening of disease progression. The present results suggest a possible role of MMN as a biomarker for NMDA receptor hyperfunction in the premanifest

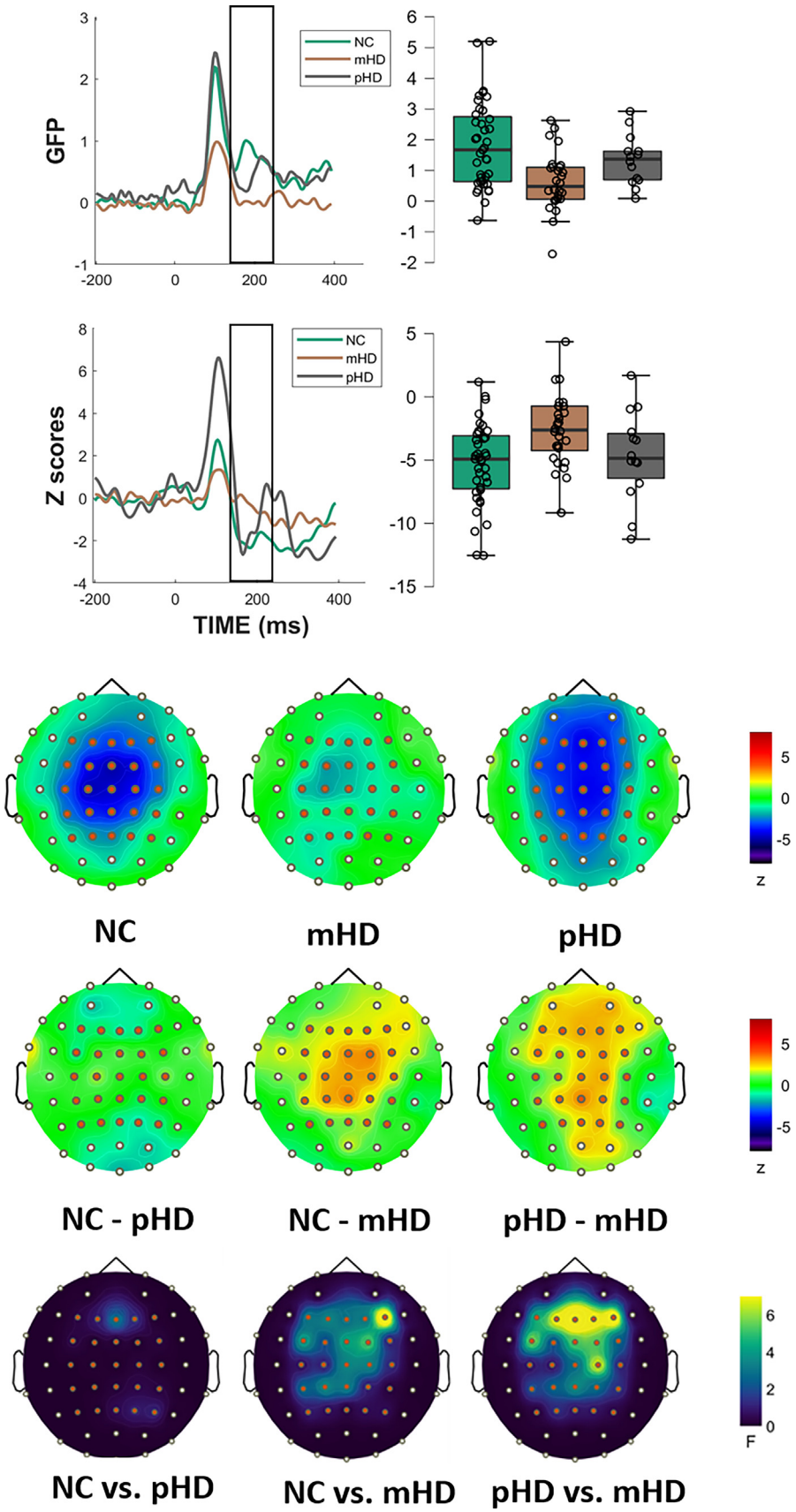

Fig. 2. The line plots show the GFP computed across the 25 processed electrodes and the mean amplitude in the ROI of three midline electrodes (Fz, FCz, Cz). The box plots illustrate the maximum amplitude of the GFP and EEG MMN activity in the 150–225 ms time window. The scalp topographies depict EEG MMN activity, group differences, and group contrasts of activity computed for each electrode at the time of the peak maximum. F values greater than 6.5 were significant, with a critical α of 0.016. Red dots depict the 25 recording positions processed for the present experiment.

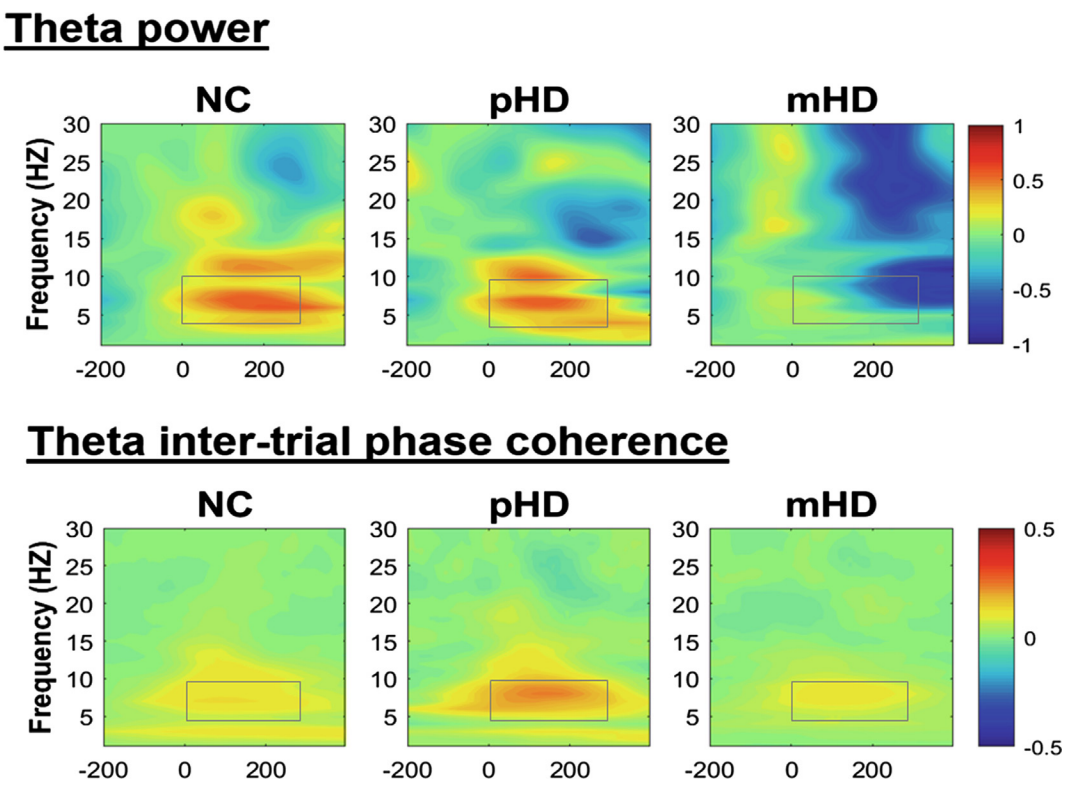

Fig. 3. Depiction of Mismatch Negativity (MMN) time–frequency power and inter-trial phase coherence for frequencies between 1 and 30 Hz over time. NC: Normal Controls, pHD pre-manifest Huntington's disease patients, mHD manifest Huntington's disease patients.

phase. In parallel to the initial deterioration of primary sensory processing, a crucial phase of changes in cortical oscillatory properties could act as a compensatory phenomenon. This hypothesis is only speculative, but it could be of help for prospective multicenter studies.

Conflict of interest

No author declares conflict of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2024.03.020.

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