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Clinical Study

Reduced automatic frontal response to auditory deviance in Huntington's disease as indexed by magnetic mismatch negativity

Chia-Hsiung Cheng [a,f], Bing-Wen Soong [b,g], Wan-Yu Hsu [a,f], Yung-Yang Lin [a,b,c,d,e,f,g,*]

[a] Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan
[b] Department of Neurology, National Yang-Ming University, Taipei, Taiwan
[c] Institute of Physiology, National Yang-Ming University, Taipei, Taiwan
[d] Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan
[e] Brain Research Center, National Yang-Ming University, Taipei, Taiwan
[f] Laboratory of Neurophysiology Taipei Veterans General Hospital, Taipei, Taiwan
[g] Department of Neurology, Taipei Veterans General Hospital, No.201, Sec.2, Shih-Pai Road, Taipei 112, Taiwan

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ABSTRACT

Huntington's disease (HD) is a neurodegenerative disorder accompanied by a degradation of dopaminergic receptors. It is evident that dopaminergic dysfunction leads to attention deterioration. However, little is known about the functional integrity of involuntary attention processing in patients with HD. The present study aimed to investigate whether patients with HD exhibit a deficit in automatic deviance detection that can be indexed by magnetic mismatch responses. Magnetoencephalographic responses during a passive oddball task were recorded to examine automatic neural activation to auditory deviants in patients with symptomatic HD and age and sex-matched healthy volunteers. The mean amplitude and peak latency of magnetic mismatch responses were calculated from the waveforms in each hemisphere. Furthermore, minimum current estimate (MCE) was applied to estimate the source strength of temporal and frontal mismatch responses. Compared with healthy participants, patients with HD exhibited a decreased waveform amplitude and a prolonged peak latency of magnetic mismatch responses in the left temporal lobe. The MCE analysis also revealed significantly lower activation of the bilateral frontal mismatch responses in patients. In conclusion, the frontal underactivation to occasional auditory deviance suggests a deficit of involuntary attention switching in HD.

1. Introduction

In addition to motor symptoms, cognitive deficits are also inherent characteristics of Huntington's disease (HD) [1,2]. Although working memory, error processing and attentional control are important in executive function tasks, [3,4] little is known about basic cognitive elements in patients with HD. In fact, a fundamental disturbance of attention may have a detrimental influence on higher-order function [5].

Attention deficits have been documented in patients with HD [5]. However, neuropsychological evaluations of voluntary attention capacity are often confounded by motor slowness or a lack of concentration, making it difficult to interpret the data. Thus, an objective assessment of involuntary attention processing may provide a new understanding of the earlier phase of attention mechanisms. Mismatch negativity (MMN) or its magnetic equivalent (MMNm) are particularly suitable for assessing the functional integrity of automatic deviance detection [6–10]. It has been proposed that the mismatch responses are generated by temporal and frontal cortices. The temporal MMN/MMNm is associated with the formation of auditory sensory memory, while the functional significance of frontal MMN/MMNm reflects the involuntary switching of attention to sound changes [11–13]. Although both electroencephalography (EEG) and magnetoencephalography (MEG) offer excellent temporal resolution, MEG has superior spatial resolution in terms of source reconstruction and has been widely employed for the evaluation of mismatch responses in different cortical generators, such as the temporal and frontal areas [10,14,15].

The cerebral blood flow of HD patients is reduced in the frontotemporal regions. Furthermore, HD is associated with changes in neurotransmitter systems, including reductions in the density of

* Corresponding author. Tel.: +886 2 2875 7398; fax: +886 2 2875 7579.
E-mail address: yylin@vghtpe.gov.tw (Y.-Y. Lin).

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dopamine receptors in the striatum and frontotemporal regions [16]. Consistent with the above findings, an association between dopamine and frontal MMN activity has been described in young healthy adults [17]. Therefore, in this study, we used a whole-head 306 channel MEG to measure temporal and frontal MMNm activities and their correlations with clinical profiles in HD patients.

2. Methods

2.1. Subjects

Due to the artifacts of dental works on magnetic signals, we finally recruited eight (out of 10) molecularly verified, right-handed, symptomatic HD patients (age 45.9 ± standard error of the mean [SEM] 2.4 years, three women) from the Department of Neurology at Taipei Veterans General Hospital. Table 1 lists the demographic information of all patients, including mean duration of illness, CAG repeat length and Unified Huntington's Disease Rating Scale (UHDRS) clinical score. Eight right-handed healthy volunteers (age 47.5 ± SEM 2.5 years, two women) were enrolled as controls, and had no hearing deficits or neurological or psychiatric disorders.

The Ethics Committee of the Taipei Veterans General Hospital, Taipei, Taiwan, approved this study. Each participant provided informed consent prior to the experiment.

2.2. Auditory stimuli and experimental procedures

The stimuli were 1000 Hz sine wave tones (including 5 ms rise and fall times), binaurally delivered at an intensity of 65–70 dB above the subject's hearing threshold through plastic earphones. The oddball block consisted of frequent standard stimuli (100 ms duration, 85%) and infrequent deviant stimuli (50 ms duration, 15%) with a stimulus onset asynchrony of 500 ms. Stimuli were presented in a pseudo-randomized fashion, such that deviant stimuli were separated by at least one standard stimulus. In each block, at least 100 deviant stimuli were collected for further analyses. All the subjects were instructed to concentrate on a self-chosen silent movie and to ignore the auditory stimuli during MEG measurement.

2.3. MEG recordings

Auditory magnetic signals were acquired using a whole-head 306 channel MEG (Vectorview, Elekta Neuromag, Helsinki, Finland) with 102 identical triple-sensor elements. Each triple-sensor element consists of two orthogonal planar gradiometers and one magnetometer. In this study, we analyzed the data from planar gradiometers which detect the largest signal directly above the activated cerebral areas [18]. Four head position indicator (HPI) coils were attached to the scalp at known locations, and a three dimensional digitizer was used to determine the anatomical landmarks of the head with respect to HPI coils.

MEG recording epochs were 530 ms with a 50 ms pre-stimulus baseline. The online recording bandpass filter and sampling rate were 0.1–130 Hz and 400 Hz, respectively. Electrooculograms (EOG) attached above the left orbit and below the right orbit were used to monitor eye movements. We discarded noise contaminated by large eye-blink artifacts (EOG >150 μV). To reduce the brain artifacts originating inside the helmet and external interferences outside the sensor array, we applied Maxwell filtering of the Neuromag software system (Vectorview, Elekta Neuromag) based on "signal space separation" theory [19]. The length of raw data buffer and subspace correlation limit were set at 7 s and 0.98, respectively [20]. The final responses were digitally filtered offline with a bandpass of 1–30 Hz [11,21].

2.4. Sensor and source analysis of MMNm

We subtracted the responses to standards from those to deviants and identified the waveforms of MMNm. At the sensor level, two gradiometer channels showing the maximal responses over each hemisphere were selected. Then the peak latency and mean amplitude of a 50 ms period (25 ms before and after the MMNm peak) were obtained at the determined gradiometer channels which showed the maximal responses over each hemisphere.

The minimum current estimate (MCE) (L1-norm) technique was used to estimate the neural activations underlying MMNm [18,22]. MCE explains the measured signals with a current distribution that minimizes the sum of current amplitudes, [22] and the results are in agreement with those obtained by multi-dipole modeling [22,23]. The source space was divided into four regions of interest (ROI): left temporal cortex (LT), right temporal cortex (RT), left frontal cortex (LF) and right frontal cortex (RF), which are well demonstrated to be involved in the MMNm processing [24,25]. The ROI were non-overlapping ellipsoids with a radius of 15 mm. We applied a standard boundary element model as a template for this analysis and employed 30 singular values for regularization.

The time window of MMNm signals in these ROI was 100–300 ms after the onset of stimulus, and the peak latency and peak strength of the maximal activation in each ROI were obtained. MCE source analysis was successfully carried out for all 16 participants.

Table 1
Demographic and clinical data of each Huntington's disease patients

			Disease duration		UHDRS score		
	Age	Sex	years	CAG repeat length	Motor	Independence	Functional
HD group							
1	48	M	3	48	38	80	7
2	41	M	1	41	56	70	4
3	48	M	1	48	50	50	1
4	49	F	6	49	39	50	1
5	46	F	5	46	33	90	11
6	48	M	8	48	25	60	2
7	55	M	3	55	29	50	1
8	32	M	7	32	26	90	10
Mean (SEM)	45.9 (2.4)	6M/2F	4.30 (0.9)	44.1 (1.5)	37.0 (4.0)	67.5 (6.2)	4.60 (1.5)
Control group							
Mean (SEM)	47.5 (2.5)	5M/3F					
Statistics	$p = 0.67$	$p = 0.59$					

F = female, HD = Huntington's disease, M = male, SEM = standard error of the mean, UHDRS = Unified Huntington's Disease Rating Scale.